Metabolism of THC

The Ingestion & Processing of Δ9-Tetrahydrocannabinol

It's widely known that **Δ9-Tetrahydrocannabinol** (**Δ9-THC**) is the active ingredient in cannabis and the primary reason people experience a psychological high. Less widely known, however, is what happens to THC in the body and how that impacts the psychological high.

What is the metabolic pathway of THC and what does that mean for its psychological effect? On a molecular level, cannabis turns into a different kind of drug when it is eaten vs. smoked, which explains its longer presence in the body. Inhalation technique also impacts bioavailability. But to understand the pathway of THC in our bodies, it's important to first understand how THC is processed.

Biochemistry

When cannabis is consumed, the liver breaks down the primary psychoactive ingredient **Δ9-THC** into other molecules. First, enzymes turn **Δ9-THC** into **11-OH-THC** (also psychoactive) and then into **11-COOH-THC** (not psychoactive.)[1]

There are a number of different versions of names for those molecule, as show below:

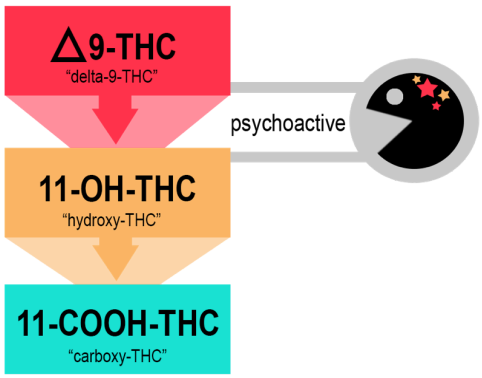
Name	Pronunciation	Notation	Also Known As:
delta-9-THC	*"delta 9 THC"*	Δ9-THC	THC
11-OH-THC	*"hydroxy THC"*	11-OH-Δ9-THC	11-hydroxy-THC
11-COOH-THC	*"carboxy THC"*	11-COOH-Δ9-THC	11-nor-9-carboxy-THC, 9-carboxy-THC, THC-COOH THC

Again, in the liver, **Δ9-THC** turns into **11-OH-THC** which turns into **11-COOH-THC**. Recall this as we examine how THC travels through the human body.

Note: The three THC molecules have different properties. For the sake of clarity they'll be referenced by their full names—**Δ9-THC**, **11-OH-THC**, **11-COOH-THC** — unless THC is meant in general.

Metabolic Pathway of THC

Whether inhaling or ingesting cannabis makes a big difference in terms of the metabolic pathway that THC takes through the body. As we will see in the sections to follow, that pathway will impact the efficacy of THC.



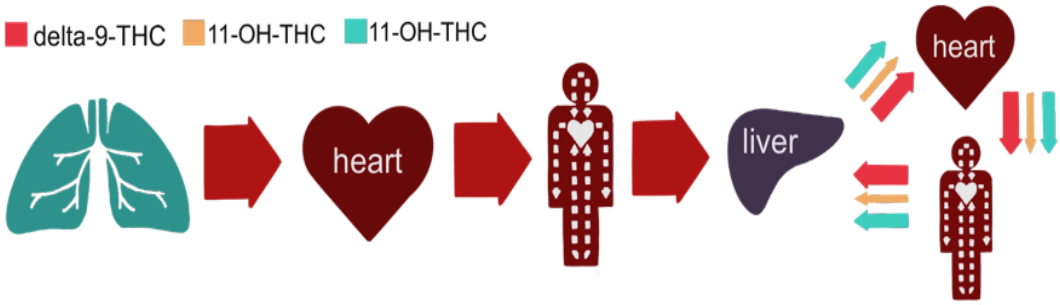
Inhalation

When cannabis is smoked or vaporized, **Δ9-THC** enters the bloodstream via absorption through the lungs. Once in the bloodstream, the **Δ9-THC** travels straight to the heart, and the heart then pumps it through the entire body—including the brain—allowing it to bind to cannabinoid receptors. The psychologically experienced high kicks in as the THC molecules pass the blood-brain barrier and bind to receptors in the brain.

There are two major kinds of cannabinoid receptors:

- **CB1 Receptors,** which are activated by **Δ9-THC** and **11-OH-THC** and found primarily in the brain and central nervous system, and
- **CB2 Receptors,** which are activated by CBN and other cannabinoids, and are found primarily in the tonsils, spleen and white blood cells.

Each time the blood circulates through the body, a certain portion of it passes through the liver. At that point, the psychoactive**Δ9-THC** is metabolized into psychoactive **11-OH-THC** and non-psychoactive **11-COOH-THC**. Afterward, these two metabolites travel along with **Δ9-THC** to the heart and from there, throughout the body. Like **Δ9-THC**, **11-OH-THC** also binds to CB1 receptors in the brain.



The biological pathway through the lungs typically results in a steep increase of **Δ9-THC** in the bloodstream within approximately 10 minutes of consumption. 11-OH-THC peaks slightly later, at around 15 minutes. After that, levels of both psychoactive molecules decrease sharply until, after 12 hours, their concentration falls under the detectable limit of 0.5 ng/ml. The second and non-psychoactive metabolite 11-COOH-THC peaks more than one hour after consumption and circulates in the bloodstream for a long time. In the quoted study it took 168 hours, i.e., 7 days, to fall under the detectable limit.[2]

Ingestion

When ingested, **Δ9-THC** enters the bloodstream through the walls of the stomach and intestines. Tests with radioactive- labeled **Δ9-THC** molecules show this process to be highly effective, with 90-95% of **Δ9-THC** molecules being absorbed, depending on the carrier medium.[3]

When absorbed gastro-intestinally, **Δ9-THC** travels first to the liver where most of it is eliminated or metabolized before it has ever had a chance to activate a receptor. After this first pass through the liver, the remaining **Δ9-THC** – and both its metabolites – go to the heart and from there into circulation. **Δ9-THC** and **11-OH-THC** reach the brain simultaneously.

Bioavailability

How much of the consumed THC actually makes it into the bloodstream? There is no easy answer. The fact is that bioavailability fluctuates wildly from method to method and from individual to individual.

Inhalation

In an experiment, six test subjects smoked the exact same amount of **Δ9-THC**. Test subject Mr. Burns exhibited almost three times as much **Δ9-THC** in his bloodstream compared to Homer who showed the lowest concentration. For all test subjects the peak was within 6 to 10 minutes after inhalation.[2]

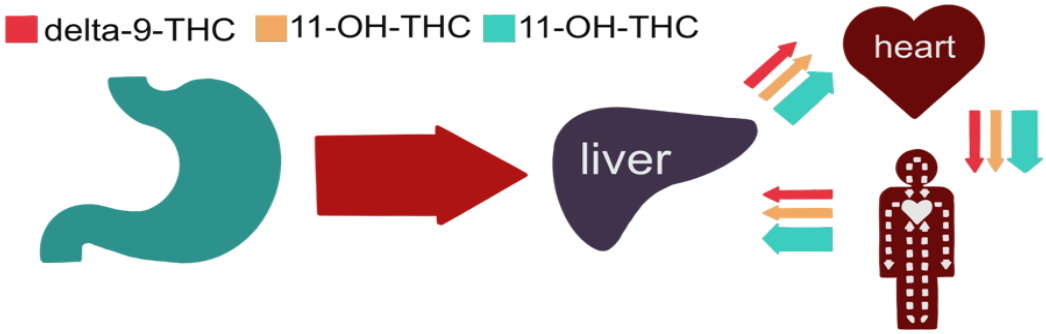
What Influences Bioavailability?

Two main factors are (1) method of inhalation, e.g., vaping or smoking, smoking in a joint or pipe, and (2) whether the test subject is an infrequent or frequent user. Technique matters, such as depth of inhalation, puff duration and breath hold increase bioavailability[3]; regular users inhale more efficiently and therefore show a 50-70% higher bioavailability of **Δ9-THC**.[4] [5]

Across all users, infrequent or frequent, the bioavailability for inhaled **Δ9-THC** is between 10-35%.[3]

Ingestion

For ingested **Δ9-THC**, bioavailability is only between 4-12%. In contrast to inhalation, the user has little influence on the degree of bioavailability, with the exception of choosing a more optimal carrier medium. In many studies the choice was sesame oil or a similar high-fat carrier. After oral use, high variability was observed not only in the absolute levels of THC but also in the timing when users show peak concentration. Concretely, Person A can exhibit peak concentration after one hour of ingestion whereas Person B can exhibit peak concentration after six hours. Multiple peaks have been reported as well.[3]



Which Produces Stronger Effects, Inhalation or Ingestion?

The following chart compares the **Δ9-THC** exposure of three different methods of intake: *inhalation*, *ingestion* and *injection*. In practice **Δ9-THC** is usually not injected, but was done so in this study as a control for determining the bioavailability of different routes. The same study suggests a mean bioavailability of 18% for inhalation and 6% for ingestion.[6]

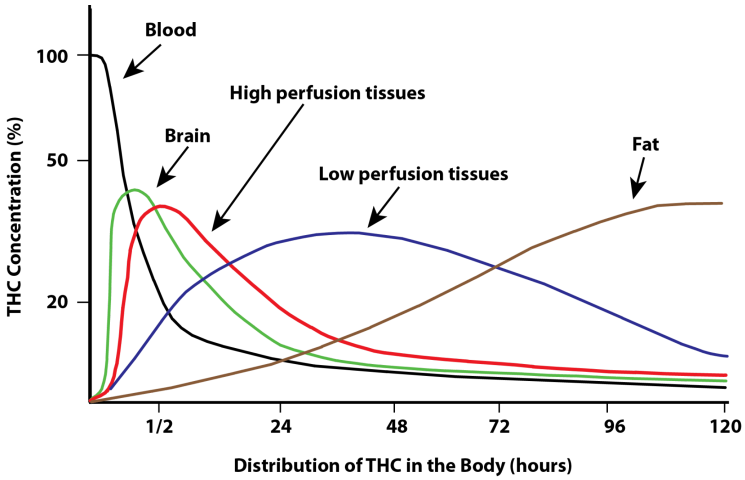
Looking at the chart below, it is tempting to conclude that inhalation produces a stronger psychoactive effect than ingestion but there are a number of problems with this assumption. First is that with bioavailability fluctuating wildly between individuals, it's difficult to determine the right dose for a fair comparison. Should you compare smoking 13 milligrams to eating 20? Or should you compare it to eating *40* milligrams, considering the much lower bioavailability of **Δ9-THC** when ingested?

Second—and more importantly—THC blood levels are a terrible indicator for the magnitude of a psychological high.

Blood may transport the THC but it's the destination that actually matters:

- **Psychoactive THC binds to CB1 receptors in the brain.** That's why a few minutes after inhalation we already see higher THC concentrations in the brain than in the blood.
- **THC is highly fat-soluble.** THC is rapidly taken up by fat tissue, where it likes to accumulate and sit for many days. From these fat deposits, THC and its metabolites are slowly released back into the bloodstream.[7]

As seen in the chart to the right[7], after smoking THC there is a time lag between concentrations in the blood and brain. That's why high THC levels in the bloodstream doesn't mean that the user experiences a psychological high at the same time.



Finally, **THC is not just THC.** Some studies suggest that the psychological high correlates better with the blood levels of the metabolite **11-OH-THC** whose absolute representation would be much lower than the one of **Δ9-THC**.[8]

Psychological High

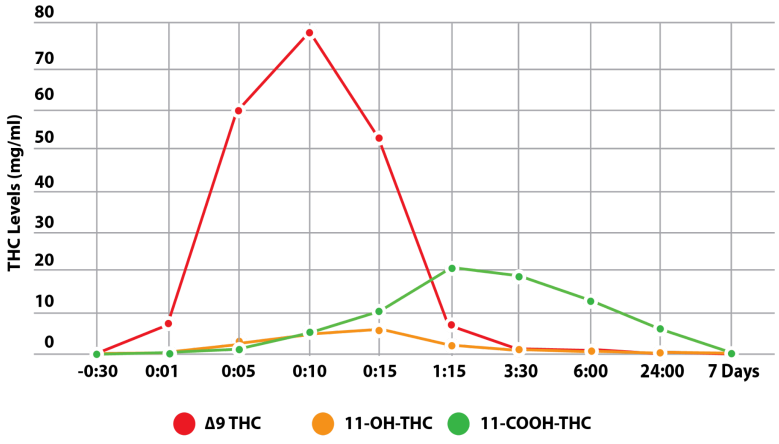
Just around the time when THC concentration is at a high point in the brain, psychoactive effects start to manifest. In the study described below, users were asked to rate the intensity of their experience over time on a scale from 1 to 10 in both inhalation and ingestion scenarios.

Inhalation

In the "*smoking*" chart below, you see the typical spike of **Δ9-THC** levels at the beginning, followed by **11-OH-THC** peaking a few minutes later (**11-OH-THC** levels are not shown). The subjectively rated effect achieves the highest level around 10 minutes after the **Δ9-THC** peak.[9]

Ingestion

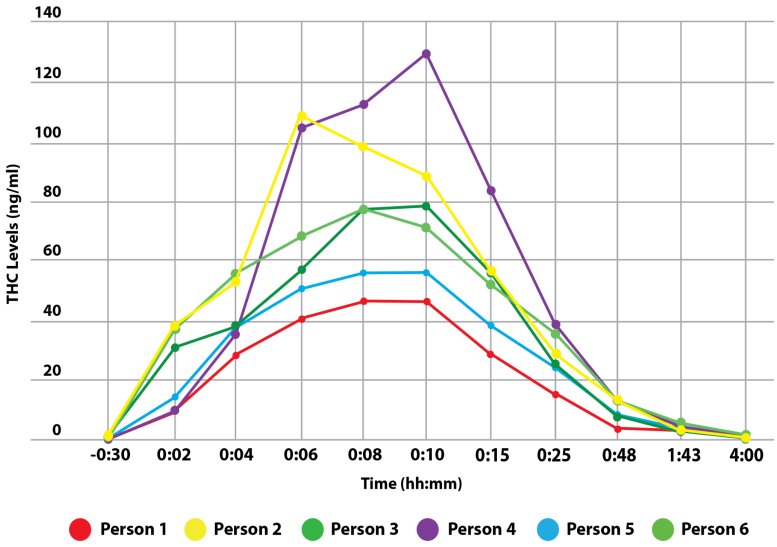
The chart to the right shows the same data for ingestion of 20 milligrams of **Δ9-THC**. Note that the time axis contains different values. Gastrointestinal absorption happens more slowly and usually results in a continuous rise and fall of blood levels and psychological high.



Keep in mind that the values represent only averages. While Person A experiences a "3", Person B might experience a "9". Therefore the chart has to be taken with a grain of salt.

Comparing the psychological high over a timescale from 15 minutes to 360 minutes (6 hours) reveals the potency of **Δ9-THC** via the pathway through the stomach.

While this study shows comparably small psychological effects for oral consumption, many others have documented a much stronger psychological high which lasted almost twice as long as in the above study (with the same dose).[8] [9]



Many users claim that edibles produce a stronger and more *"psychedelic"* effect when compared to smoking. Unfortunately, there aren't many studies that have assessed the quality of psychological effects across different methods of intake. An insight the data does provide however, is that the ratio of **Δ9-THC** to **11-OH-THC** impacts the intensity of the psychological high. *This ratio depends directly on the method of intake.*

The '*first-pass effect*' through the liver drastically changes the ratio of the two psychoactive cannabinoids. When cannabis is inhaled, blood tests show a 10:1 ratio between **Δ9-THC** and **11-OH-THC**. When cannabis is ingested, however, blood tests show this same ratio being 1:1.[8] **11-OH-THC** passes the blood-brain-barrier more easily than **Δ9-THC**. Moreover, in animal tests, **11-OH-THC** has shown to be three to seven times more potent than **Δ9-THC**, i.e., which is three to seven times more capable of binding to the CB1 receptors in the brain.[3]

Altogether, this means that the lower bioavailability of **Δ9-THC** when ingested appears to balance out with the larger occurrence of **11-OH-THC** and its greater potency in the brain.

Minimum Effective Dose

It's well established that coming up with the right *minimum effective dose* is a matter of trial and error. Bioavailability fluctuates wildly across individuals and gender, as well as many other factors. The enzymes in the liver of a man and a woman work differently, which leads to a lower rate of blood plasma being cleared in women[10], which can also impact efficacy.

So, where does one start? Some edibles sold in US states with legalized medical and/or adult usage marijuana laws, contain very high doses of 100 milligrams and more.

However, 20 milligrams resulted in a medium to strong effect across the board, suggesting that the minimum effective dose is significantly lower. For example Colorado mandates a limit of 10 milligrams of THC per edible, which is also the state's recommended dose per "*serving*".

Conclusion

There are very few studies that examine the correlation of psychological high to THC concentration in our blood. Those studies that do exist point to a better correlation of **11-OH-THC** with the high levels of psychological effects. That's important because it means achieving more with less. Micro-dosed edibles may be a *'sweet spot'* for health-conscious individuals looking for mild and enduring effects at low levels of exposure.

References

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