HempConsult

Acute Reference Dose of Δ9 -THC

General Introduction

No-Observed-Adverse-Effect Level (NOAEL)

The highest tested dose of a substance that has been reported to have no harmful (adverse) health effects on people or animals. Can apply to a particular study, species (e.g. rat, dog), or all studies on a particular substance.
(ec.europa.eu/health/opinions2/glossary/mno/noael.htm)

Lowest-Observed-Adversive-Effect level (LOAEL)

The lowest tested dose of a substance that has been reported to cause harmful (adverse) health effects on people or animals. (Agency for Toxic Substance and Disease Registry)
Contrary to No Observed Adverse Effect Level (NOAEL) and Low Observed Adverse Effect Level (LOAEL), NOELs and LOELs do not necessarily imply toxic or harmful effects and may be used to describe beneficial or other measurable biological or pharmacological effects of chemicals. (EIHA, 2015)

Acute Reference Dose (ARfD)

The acute reference dose (ARfD) is defined by the World Health Organization (WHO) as the amount of substance per kg of body weight that can be absorbed via the food with a meal or within a day without any perceptible risk to the consumer. It is only determined for substances which, owing to their acute toxicity, can cause health damage even on one-off or short-term exposure. As a rule, the ARfD value is derived from the lowest dose determined experimentally in animal experiments without a noticeable adverse effect (No Observed Adverse Effect Level, NOAEL), taking into account a safety factor of 100.

$$RfD(mg/kg/day) = \frac{NOEL(mg/kg/day)}{Uf_{inter} * Uf_{intra} * Uf_{other}}$$

Frequently, a "no-observed-adverse-effect level" or NOAEL is used in place of a NOEL. If adverse effects are observed at all dose levels tested, then the smallest dose tested, the "lowest-observed-adverse-effect level" or LOAEL, is used to calculate the RfD.
An additional uncertainty factor usually applied in these cases, since the NOAEL, by definition, would be lower than the LOAEL had it been observed. If studies using human subjects are used to determine a RfD, then the interspecies uncertainty factor can be reduced to 1, but generally the 10-fold intraspecies uncertainty factor is retained.
(https://en.wikipedia.org/wiki/Reference_dose)

Example

As an example, consider the following determination of the RfD for the insecticide chlorpyrifos, adapted from the EPA's Interim Reregistration Eligibility Decision for chlorpyrifos:

The EPA determined the acute RfD to be 0.005 mg/kg/day based on a study in which male rats were administered a one-time dose of chlorpyrifos and blood cholinesterase activity was monitored.

Cholinesterase inhibition was observed at all dose levels tested, the lowest of which was 1.5 mg/kg. This level was thus identified at the lowest observed adverse effect level (LOAEL). A NOAEL of 0.5 mg/kg was estimated by dividing the LOAEL by a three-fold uncertainty factor. The NOAEL was then divided by the standard 10-fold inter- and 10-fold intraspecies uncertainty factors to arrive at the RfD of 0.005 mg/kg/day.

Scientific Opinion on the risks for human health related to the presence of tetrahydrocannabinol (THC) in milk and other food of animal origin (EFSA, 2015)

Dose response assessment done

Studies in humans indicated that **2.5 mg Δ9-THC/day** (Editors note: Beal et al., 1997; BgVV, 1997, 2000; Ramaekers et al., 2004), corresponding to **0.036 mg Δ9-THC/kg b.w. per day** for a person with a body weight of 70 kg, **may be regarded as a lowest-observed-adverse-effect level (LOAEL)**, at which not only appetite is stimulated but also adverse central nervous system adverse effects may occur. It is also the lowest dose known to exhibit moderate adverse effects in single dose studies in healthy volunteers.

Health-based guidance value

From the LOAEL of 0.036 mg/kg b.w. per day in humans an acute reference dose (ARfD) of 1 µg Δ9-THC/kg b.w. is established by applying an overall uncertainty factor (UF) of 30. This UF takes into account extrapolation of a no observed adverse effect level from the LOAEL (factor of 3) and interindividual differences (factor of 10).

The derivation of a Tolerable Daily Intake was not considered to be necessary because ensuring that the exposure is below the ARfD would also protect against possible effects of repeated exposure.

EFSA states further:

„However, **a NOAEL referring to the described adverse effects cannot be defined up to now** and it is not known if these adverse effects occur below the lowest tested daily oral dose. **The identified LOAEL of 0.036 mg Δ9-THC /kg b.w. per day is considered to be relevant** for sensitive individuals, since it is the lowest daily dose administered in clinical studies for the therapeutical use of Δ9-THC.“

and

„The CONTAM **Panel concluded that an UF of 3 is sufficient to allow for extrapolation from the LOAEL to a NOAEL** considering that the LOAEL is based on effects of low or moderate severity. **An additional UF of 10 is required for interindividual differences** because although the data on adverse effects are partly derived from studies in patients with severe diseases, data on adverse effects in infants and children are not available and there are interindividual differences in metabolism (CYP2C polymorphism).“

Comment by HempConsult

The European Industrial Hemp Association (EIHA) points out that contrary to No Observed Adverse Effect Level (NOAEL) and Low Observed Adverse Effect Level (LOAEL) as used by EFSA, NOELs and LOELs do not necessarily imply toxic or harmful effects and may be used to describe beneficial or other measurable biological or pharmacological effects of chemicals. Effects of THC are described in the literature as temporary, mild to moderate psychomotor- or cognitive effects. These contrasts vastly with adverse (toxic) effects, which tend to be severe and chronic, such as neurotoxicity or cancerigenousity (Sarmento et al.,2015). **Therefore NOEL/LOEL are the appropriate terms in relation to THC.**

The European Industrial Hemp Association (EIHA) proposed after an extensive review of the literature on the topic of THC consumption and effects, a **Lowest Observed Effect Level (LOEL) of 2.5 mg of THC intake per person twice daily**. Due to the fact that the oral consumption of THC results in its effects wearing off latest within 8 hours, a twice daily intake was put forward, taking into account 16 hours of awakened time (Sarmento et al., 2015). **A total daily intake of 5 mg Δ9-THC (2 x 2,5 mg) results in a LOEL of 0,07 mg Δ9-THC/kg b.w. per day assuming a body weight of 70 kg.**
With regards to EFSA´s own guidelines and advice in practice an **additionally total uncertainty factor of 10 for THC** would apply (Iffland, Kruse and Carus, 2016). This UF takes interindividual differences into account and **does not use a LOAEL-NOAEL-UF** (similar to nicotine). **EIHA's standpoint is that THC is treated unequally and unnecessary strict, especially with regards to the UF for opium alkaloids, nicotine, caffeine, alcohol and vitamin E.**

From the LOEL of 0.07 mg/kg b.w. per day for a person with a body weight of 70 kg, an acute reference dose (ARfD) of 7 µg Δ9-THC/kg b.w. is established by applying an overall uncertainty factor (UF) of 10:

$$ARfD = \frac{LOEL\ mg/kg}{70\ kg} = \frac{5\ mg/kg}{70\ kg} = 0{,}07\ mg\ \Delta 9\text{-}THC/kg\ b.w.\ per\ day$$

$$= \frac{LOEL\ (mg/kg/day)}{UF\ 10} = \frac{0{,}07\ mg/kg/day}{10} = 0{,}007 = 7\ \mu g\ \Delta 9\text{-}THC/kg\ b.w$$

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Sources

https://ec.europa.eu/health/opinions2/glossary/mno/noael.htm
https://www.atsdr.cdc.gov/glossary.html
https://en.wikipedia.org/wiki/Reference_dose

EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2015. Scientific Opinion on the risks for human health related to the presence of tetrahydrocannabinol (THC) in milk and other food of animal origin. EFSA Journal 2015;13(6):4141, 125 pp. doi:10.2903/j.efsa.2015.4141

Sarmento, L., Carus, M., Grotenhermen, F., Kruse, D., Brenneisen, R., Grassi, G., 2015. Scientifically Sound Guidelines for THC in Food in Europe.