EIHA contribution on maximum levels for THC in food

Hemp has been a **traditional food source** for thousands of years and all parts of the plant, except stems, have been consumed, both in Europe and abroad. In the pre-industrial era, hemp oil was one the most consumed vegetable oils in the human diet. Modern food business operators have been producing and trading hemp food in our continent for decades: as recorded in a survey requested by the Commission in 1997, multiples tonnes of hemp food were already present on the market at that time[1].
Furthermore, hempseeds are particularly rich in **high-quality proteins** and have a **unique essential fatty acid spectrum**. A shift in consumers' trends towards healthy diets led to a **strong increase of hemp food demand**, resulting in a significant development of the supply chains.

Cannabinoids are natural constituents of the plant Cannabis sativa L. and its raw materials (i. e. seeds, leaves) derived therefrom, and not to be regarded as contaminants.
For the residual contents of **natural constituents** to be limited in food we propose the term **"residual natural constituents"**. By this we define the residual level that shows in hemp food after certain (industrial) processing measures.
Food derived from hemp contains traces of a cannabinoid which is the psychoactive substance **tetrahydrocannabinol** (delta9-THC), and which remains in the food even after the most careful cleaning processing, being a residual natural constituent of hemp.

Hemp, hempseeds and food products are:

- **traditional**, because they have a thousand of years of history as food in Europe;
- **innovative**, because they were just rediscovered in the last decades;
- **healthy**, because of their unsaturated fatty acids content, a perfectly balanced ratio of the fatty acids Omega-3 and Omega-6, the content in easy digestible proteins as well as vitamins and trace elements;
- **safe**, because all hemp food products are derived from **industrial hemp with very low THC levels (from EU certified hemp varieties)**.

At the EU level, the Health Based Guidance Value (HBGV) **for THC intake from food recommended by EFSA is outdated and unnecessary strict**. Based on a biased consideration of past studies, the assessment led to an unnecessary strict and obsolete result (TDI/ARfD of 0.001 mg/kg bw). The difference is particularly striking if compared to the HBGV's of our international competitors, like Canada (0.014 mg/kg bw), Switzerland (0.007 mg/kg bw) or Australia and New Zealand (0.006 mg/kg bw). Indeed, the guidance value for THC recommended by EFSA, upon which the Council will most probably base its decision on THC limits in food, is based on wrong conclusions of studies and data in many respects.
In particular, **we would like to highlight the following biases** of the EFSA guidance on THC:

- The LOAEL of 2.5 mg of delta9-THC, defined by EFSA and BfR for effects on the central nervous system, is derived from only a few clinical studies or trials, respectively, results of which are not conclusive. The whole ensemble of clinical and observational **studies on THC shows that the LOAEL is to be at least set at 5 mg per day and adult**.

[1] Hempseeds: ca 200 tonnes; Hempseed oil: ca 33,000 litres; Hemp ready made products (snacks, flour, muesli, bread, bakery & pasta): ca 55 tonnes; Drinks with hemp flowers/leaves: ca 115,000 litres; Snacks with hemp flowers ca 2 tonnes

- The overall **uncertainty factor (or safety factor) of around 36** applied to the LOAEL for deriving a **Health Based Guidance Value (HBGV) for THC is set much too high** for such a substance of relatively low acute toxicity, compared to other substances (toxins) of concern in food or consumer products such as alcohol, caffeine, nicotine, glycoalkaloids (e. g. solanine) or morphine (from poppy seeds). There is no scientific evidence that sub-psychoactive levels of THC on foods have any significant effects on human health. During the last 50 years, the threshold amount of THC that is required for psychoactivity has been carefully studied in humans and is quite well known by now. Aside from the mild psychoactivity effect in most humans when taken orally 5 mg of THC or more, there are no other physiological or psychological effects that can be ascribed to low amounts of THC that are below the psychoactive threshold. Hence, the Acute Reference Dose (ARfD) **or HBGV of 1 µg/kg bw**, proposed by EFSA in 2015, is unnecessarily low and not justified from a modern scientific viewpoint.
- The **health authority for Australia and New Zealand (FSANZ)** has derived a dose of 5 mg THC per day as LOAEL in a re-examination (2011) of its careful risk assessment of THC in food. On this basis a **HBGV of 6 µg/kg bw** was derived for THC.
- The **Swiss Federal Office of Public Health (SFOPH)** had derived a **HBGV of 7 µg/kg bw** on the basis of various studies, also using a LOAEL of 5 mg/d of THC per adult person.
- **Croatia** is also an EU country with an up-to-date HBGV at the higher level.

Based on scientific studies and on experience, a HBGV of delta9-THC may reach up to 7 µg/kg bw (or 490 µg per day and adult).

On these grounds, **the DRAFT values for maximum levels for THC in food suggested by the European Commission** (Working Group "Agricultural Contaminants") in the context of a stakeholder consultation **are unnecessarily low, not supported by scientific evidence and unacceptable.**

Considering all the above and the "**Scientific Discourse on Lowest Observed Adverse Effect Level (LOAEL) and Acute Reference Dose (ARfD) of delta9-THC and their impacts on thresholds for hemp food"** (Annex) the EIHA request for thresholds is:

Food	**Maximum level for THC (*) mg/kg**	**Alternatively: Guidance value for THC (*) mg/kg**
Hemp seeds	10	10
Ground hemp seeds (hemp seed powder), (partially) defatted hemp seed (press cake) (hemp seed flour), hemp seed bran	10	10
Hemp seed oil	20	10

(*) the maximum level and the guidance value refer to the sum of Δ9-tetrahydrocannabinol (Δ9-THC) and Δ9-tetrahydrocannabinolic acid (Δ9-THCA)

Based on **appropriate consumption data** for hemp containing food, correspondingly **higher guidance values for THC in food (raw material, see table above) and ready-to-eat food products and food supplements** are derived (see table below):

Table 1: New EIHA proposal resulting in a daily total THC uptake of 500.55 µg

Food categories	EIHA Guidance value for total THC [µg/kg]	Average Consumption Pattern [g/day/person]	Total THC uptake/day/person (consumption * guidance value = uptake) [µg]	Current Guidance values (Germany – BfR) [µg/kg]
Edible oils	10 000	2.93	29.30	5 000
'High Volume' foods: Protein (e.g. Tofu, hemp based dairy alternatives)	1 000	183.87	183.87	150
'High Volume' foods: Carbohydrates (Bread, Baked Goods, Pasta, Breakfast Cereal)	1 000	230	230	150
'Low Volume' foods (Protein Shakes, Sweets)	1 000	27.01	27.01	150
		[ml/day/person]		
Alcoholic beverages (Beer, Wine, Spirits)	20	180.61	3.61	5
Non-heated Non-alcoholic beverages (Soft Drinks, Fruit Juices)	20	120.03	2.40	5
Heated Non-alcoholic beverages (Tea, Infusions)	80	304.47	24.36	5
Total THC daily uptake			500.55	

Table 2: List of new total-THC-reference values (green box) for hemp ingredients derived from EIHA proposal on ready-to-eat products, selected recipes and consumption patterns; together with guidance values and limits for listed countries.

Ingredients	EIHA proposal 2017 Total THC [µg/kg]	THC Guidelines	THC limits[4]		
		Germany – BfR [µg/kg] (total THC) 2000	Switzerland [µg/kg] 2016	Canada [µg/kg] 1998	Australia and New Zealand [µg/kg] 2017
Hemp Seeds Whole or Hulled	10 000	–	10 000	10 000	5 000
Hemp Seed Oil (Edible oil)	10 000	5 000	20 000	10 000	10 000
Processed Press Cake (Protein powders, Flour)	10 000	–	–	10 000	5 000

Tables 1 and 2: Proposals for THC guidance values in food (from EIHA Position Paper, 2017, www.eiha.org)

Addendum:

For food supplements, an allowable maximum daily intake of 490 µg of total-THC is proposed.

The proposed guidance values are not to be meant as legally binding limits, whereas maximum limits are understood as proposals for legally binding values.

In this context, total THC is the sum of delta9-THC and delta-9-tetrahydrocannabinol carboxylic acid (THCA) as determined by analysis and **normalized by calculation to delta9-THC**. THCA, the natural form of THC that is produced by the hemp plant, is not orally active and cannot enter the central nervous system by consuming hemp foods. For this reason, it would not be reasonable to establish legally binding food THC limits according to the total THC with the constituents THC plus THCA that occur in hemp foods as natural constituents. However, the above guidance values are proposed as **total-THC values for practical reasons** and **could be accepted by industry only on these grounds:** comparability with historical values, easier analytical measurement, and possible (part-)decarboxylation of the corresponding acid on prolonged exposure to elevated temperatures.

However, when it came to fixing **legally binding limits for THC**, we could **only accept maximum limits for delta9-THC** (without the corresponding acid THCA), if there were a **validated analytical method** in place (preferentially some type of High Performance Liquid Chromatography) which would separate these two chemical compounds and allow their separate quantitative measurement. This analytical method should be binding for all Member State authorities.

As such a legally binding analytical method was also possible to establish for the measurement of total-THC (by Gas Chromatography) in the hemp field samples (see CDR 2017/1155, Annex I) this should also be possible for a state-of-the-art analytical method for quantification of the psychoactive constituent delta9-THC in food and feed.

Questions and Remarks on the EU COM Proposal, which need to be discussed and considered in in the further course of the consultation:

1. Why are the proposed limits set for total-THC? (Total-THC as sum of delta9-THC and the non-psychotropic delta9-THCA). Total-THC includes THCA and because of that the proposed limits are much too low. They have to be doubled at least, if not tripled. For example, it will be practically impossible to comply with the limit for whole (unpeeled) hemp seeds. There is no risk assessment at all by EFSA on THCA as a natural constituent of hemp food, and there is no HBGV for delta9-THCA. The EFSA risk assessment was for delta9-THC (acid-free) only. The reason is quite simple: EFSA's Scientific Opinion (2015) could only refer to delta9-THC because all the studies used for EFSA's derivation of the ARfD of delta9-THC (1 µg/kg bw*d) had been performed with Marinol or pure delta9-THC (INN: Dronabinol, acid-free). Thus, scientifically based limits can be given for delta9-THC (acid-free) only, not for total-THC.
2. How is the sum of delta9-THC and delta9-THCA defined by the EU COM? Will delta9-THCA be normalized to delta9-THC?
3. Are there official, validated analytical methods in place for all European authorities and national laboratories for quantitative determination of THC and THCA, including

analytical LOQ (Limit of Quantification)? Since there is no standard analytical method for governments in the EU to follow for the analysis of ppm amounts of THC and THCA in foods, such minimal levels must not be set too low, because it will be impossible for such low levels to be analysed with accuracy and precision throughout the EU by a wide variety of methods that do not follow one specific procedure. In other words, we need higher levels to allow some tolerance and room for human error in the results.

4. Why is this proposal not in line with Commission Recommendation 2016/2115 on the monitoring of the presence of delta9-THC, its precursors and other cannabinoids in food?

5. Are there no maximum levels given for other foodstuff because for the latter it is intended to apply Article 2 of Reg (EC) 1881/2006 using a dilution factor for calculation of the (lower) max. limit in the food containing (a) hemp seed (derivative)?
   If this procedure were meant, it would not be acceptable at all in the context of the proposed extremely low THC limits in the EU COM Agri proposal. (see Reg (EC) 1881/2006 Art. 2, para 3. on compound foodstuff). On this point, EIHA requests detailed explanation what is meant by application of Art. 2 of the Regulation.

EIHA represents the common interests of hemp farmers, producers and traders working with hemp fibres, shives, seeds, leaves and cannabinoids. Our main task is to serve, protect and represent the hemp sector in the EU and international policy-making. We cover different areas for the application of hemp, namely its use for construction materials, textiles, cosmetics, feed, food and supplements.

Annex

Scientific Discourse on Lowest Observed Adverse Effect Level (LOAEL) and Acute Reference Dose (ARfD) of delta9-THC and their impacts on thresholds for hemp food

1. Critical review of EFSA's and BfR's derivation of Lowest and No Observed Adverse Effect Levels for THC as a basis for a Health Based Guidance Value

The discussion in publications on scientific and legal aspects of the toxic doses of THC in oral food consumption already reveals a strong discrepancy between the doses of THC recognised in many studies as intoxicating and the LOAEL (Lowest Observed Adverse Effect Level) of 2.5 mg/d for THC used today by authorities to derive an ADI (Acceptable Daily Intake) for the substance.
An intoxicating dose of THC is at least 5 mg all at once, but mostly 10 - 20 mg THC per day in adults, as reported, for example in a recently published review[1] .

The lowest dose of THC at which an adverse effect has been observed in animal or human studies, known as the LOAEL (Lowest Observed Adverse Effect Level), as used by the BfR and EFSA for the derivation of a HBGV (Health Based Guidance Value)[2], is supposed to be 2.5 milligrams of THC per day and adult. It is an extremely low value, which, however, cannot be derived from the most relevant scientific studies.

The BfR guideline value (recommendation) for the maximum daily intake of total THC[3] of 1 to 2 micrograms per kilogram of body weight (µg/kg bw) has as its scientific basis only one single study from the period before 1997 on 31 AIDS patients[4]. In a report on THC levels in food in 2018[5], the BfR then simply confirmed that it also recognised the Acute Reference Dose (ARfD) of 1 µg Delta-9-THC/kg bw recommended by EFSA in 2015 as a precautionary value.

However, the LOAEL of 2.5 mg delta9-THC/d derived by EFSA from a small number of studies and the Acute Reference Dose (ARfD) derived from it are worth a discussion in depth.
EFSA mainly uses three large clinical trials in HIV patients (Beal et al. 1995[6] and 1997[7], Struwe

[1] Lachenmeier et al., Foods containing hemp - an update, Deutsche Lebensmittel-Rundschau 115 (2019), 351-372, see chapter „Forensisch-toxikologische Beurteilung", p. 355, right column.
[2] 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
[3] Total THC is according to BfR definition: "The above values refer to the food ready for consumption and apply to total THC including delta-9-tetrahydrocannabinol carboxylic acid". See :https://www.bfr.bund.de/de/presseinformation/2000/07/bgvv_empfiehlt_richtwerte_fuer_thc__tetrahydrocannabinol__in_hanfhaltigen_lebensmitteln-884.html (accessed 18.09.2020).
[4] Deutsche Forschungsgemeinschaft, Lebensmittel und Gesundheit II, Sammlung der Beschlüsse und Stellungnahmen (1997-2004), Mitt. 7, Kap. 25, Δ⁹-Tetrahydrocannabinol (THC) in Hanfprodukten, p. 172 ff.
[5] BfR: Tetrahydrocannabinol levels are too high in many food products containing hemp - adverse health effects are possible, BfR opinion no. 034/2018 of 8 November 2018, p. 14.
[6] Beal et al., Dronabinol as a Treatment for Anorexia Associated with Weight Loss in Patients with AIDS, J. Pain Sympt. Managem. 10(2), Feb 1995:89-97.
[7] Beal et al., Long-Term Efficacy and Safety of Dronabinol for Acquired Immunodeficiency Syndrome-Associated Anorexia, J. Pain Symptom Management 14(1), July 1997:7-14.

et al. 1993) to determine the LOAEL, and one very small study (11 subjects)[8] which was the only one to specifically and systematically investigate the psychoactive effects of delta9-THC, whereas in the clinical trials, the adverse CNS side effects were only documented in the usual system for recording adverse effects.

EFSA summarises the outcome of its investigation as follows:
"Overall, the CONTAM Panel identified 2.5.mg per person as the lowest observed adverse effect dose of Δ9-THC orally administered in a single dose study. At this dose, single exposure in healthy volunteers had moderate effects (increased sedation, altered scale scores in the POMS, slightly impaired working memory performance and reduced diastolic blood pressure) (Ballard and Wit, 2011) (see Section 7.5.1.3).
Also in repeated dose studies the lowest dose of Δ9-THC orally administered to humans identified by the CONTAM Panel was 2.5 mg/person per day. This dose was applied in a trial for the treatment of anorexia related to AIDS for a 6-week period (Beal et al., 1995) and a 12 month period (Beal et al., 1997), and in a trial in HIV-infected patients with weight loss (Struwe et al., 1993). In these studies adverse effects associated with oral Δ9-THC doses of 2.5 mg Δ9-THC twice a day (5 mg Δ9-THC/day) or a single dose of 2.5 mg Δ9-THC/day were reported (see Section 7.5.1.3).
Therefore, 2.5 mg Δ9-THC/person per day may be regarded as a lowest observed adverse effect level (LOAEL). Indications in fact sheets for medical uses are in accordance with this (FDA, 2004; Haenseler, 2014) (see Section 7.5.1.2)."

However, this conclusion cannot be agreed to after a careful study of the original papers. The original publications on the results of the clinical trials do not even allow the conclusion to be drawn that CNS side effects already occurred at a dose of 2.5 mg delta9-THC/d, because in these trials side effects are only documented for the entire patient collective, and most of them were given 5 or 10 mg/d of Dronabinol[9] to achieve the desired effect (see Beal et al, 1995):
"The main increase in appetite to end point for evaluable patients receiving dronabinol was 38% over baseline, compared with 8% for those receiving placebo (P-- 0.015). Interestingly, in the 11 patients [of 72 evaluable patients] who, due to side effects, decreased their dose of dronabinol to 2.5 mg once daily, the appetite increase was the same as for those taking medication twice daily."
The same study showed that a dose of 2.5 mg delta9-THC was tolerated by all patients without side effects (as opposed to double dose):
"Dronabinol was well tolerated. Most side effects reported were central nervous system disturbances that are commonly associated with cannabinoids. In most cases, they were not severe enough to warrant intervention. There was no significant difference between both treatment groups in the patient dropout rates due to adverse reactions. Six Dronabinol versus three placebo recipients discontinued therapy due to any adverse effect thought to be

[8] Ballard, M.E., de Wit, H. Combined effects of acute, very-low-dose ethanol and delta(9)-tetrahydrocannabinol in healthy human volunteers (2011), Pharmacol. Biochem. Behav. 2011 February; 97(4): 627-631. doi:10.1016/j.pbb.2010.11.013.
[9] Dronabinol is the INN of the pharmaceutical active ingredient (-)-trans-Delta9-Tetrahydrocannabinol (delta9-THC) which by its chemical structure is identical to the THC naturally occurring in hemp. For avoidance of doubt, this delta9-THC is free from delta-9-tetrahydrocannabinol carboxylic acid, and not to be confused with total-THC (the latter often simply called "THC"). Total-THC is the sum of delta9-THC and delta-9-tetrahydrocannabinol carboxylic acid, normalized by calculation to delta9-THC.

possibly or probably related to treatment. These numbers are small and attest to the safety and tolerance of treatment. Most patients who required dose reduction were able to tolerate the half-dose (one 2.5-mg capsule in the evening). Of 17 patients who received a reduced dose, 11 were evaluable for efficacy and showed a similar appetite increase..."

Moreover, the evaluability of this study is restricted as "*commercially available or investigational antiretrovirals were allowed*" meaning that the assignment of any observed side effects to a specific drug (here THC) becomes questionable.

The attribution of any observed side effects on the CNS (central nervous system) to THC only becomes even more questionable because nowadays it is known that "HIV-associated neurocognitive disorder (HAND) affects nearly half of all HIV-infected individuals. "*Synaptodendritic damage correlates with neurocognitive decline in HAND, and many studies have demonstrated that HIV-induced neuronal injury results from excitotoxic and inflammatory mechanisms*"[10]. Thus HIV-symptoms of the patients in the cited Dronabinol trials could have been confused with THC side effects (such as cognitive impairment, for example).

A review by Plasse et al. [11] on the clinical experience with Dronabinol states "the lowest rates of termination for side effects were in the 2.5 mg ... groups, only 1 patient in each group" [8 to 9 patients per group] i. e. maximum of 12 % of patients had side effects; and: "*Many of the side effects reported may have been related to underlying disease or concomitant medications rather than to dronabinol.*", and "*Drowsiness and sedation are often related to other concomitant medications and the stress of disease and therapy together.*"

Also, the long-term study by Beal et al. (1997) does not show that the undesirable side effects would have already occurred at a dose of 2.5 mg/d (again, patients received between 2.5 and 20 mg delta9-THC/d):

First, it should be noted that 90% of the patients received 5 mg/d of THC (dronabinol), and only 10% received 2.5 mg/d of THC; 19% of the patients even increased their dose to 7.5 mg/d:
"*Ninety percent of the patients enrolled in the study received an initial daily dronabinol dose of 2.5 mg orally twice daily, and the remaining 10% received 2.5 mg orally once daily in the evening. Thirty-eight percent of patients modified their dronabinol dose during the study. One-half of these patients increased their dose, most commonly to 2.5 mg during the day and 5 mg with supper or at bedtime (total 7.5 mg daily). Two patients increased their dronabinol dose to 5 mg twice daily and another from 5 mg twice daily to 5 mg twice daily plus 10 mg at night (total 20 mg daily). The other one-half decreased their dose from 2.5 mg twice daily" to 2.5 mg at bedtime.*"

As to the effects of these doses it is reported: "*As expected, adverse events were primarily related to the central nervous system ... [series of symptoms] ...and occurred in 35 of 93 patients (38%) enrolled in the study.*"

[10] M. Wu et al., Druggable targets of the endocannabinoid system: Implications for the treatment of HIV-associated neurocognitive disorder, Review, Brain Res. 2019, Dec 1, 1724: 146467.
[11] Plasse et al., Recent clinical experience with Dronabinol, Pharmacol. Biochem. Behav. 1991 Nov; 40(3): 695-700.

In the publication there is nothing more specific reported on the side effects, and these have not been broken down to the individual dosing groups.

In Gorter et al (1992), the THC dose was reduced from 7.5 mg/d to 5 mg/d as a minimum dose (not 2.5 mg!) to minimize side effects:
"Patients were treated with dronabinol (Marinol®, Roxane Laboratories, Columbus, Ohio, USA) at a starting dose of 2.5 mg orally three times daily. Doses, which were adjusted to minimize side-effects while stimulating appetite, ranged from 2.5 mg twice daily to 5 mg four times daily. Most patients were continuing treatment at the time of this analysis; the median duration of treatment was ≥12 weeks (range, > 4to >20 weeks). All patients tolerated therapy well. They were able to adjust the medication dose to avoid unwanted THC side-effects, such as sedation and persistent euphoria. No patient discontinued therapy because of side-effects."

The placebo-controlled study by Struwe et al. (1993)[12] with only 12 patients does not show that the CNS side effects already occurred at a dose of 2.5 mg delta9-THC/d for most or all patients; only one patient had to reduce to 2.5 mg of THC twice daily, and one other patient to 2.5 mg per day only. These two patients "*did not tolerate Dronabinol, even following dosage reduction, and withdrew during the first period [5 weeks] because of mood altering effects and sedation.*" All the other patients tolerated even 5 mg twice daily (i.e. 10 mg/d) in order to achieve the desired effect.
However, one has to be cautious to attribute the side effects with the two HIV patients to the dronabinol treatment alone, as already explained above.

The EFSA CONTAM Panel claims in its "Scientific Opinion (2015, p. 64) that in the studies mentioned (Beal et al., Struwe et al.) adverse effects of THC occurred not only at 5 mg/d but also at 2.5 mg/d.
However, the study of the original publications by Beal et al. reveals that such effects were not detected at 2.5 mg/d, or that they were not assigned to a patient collective with this dose, or that higher doses were actually administered, and no adverse effects were reported for the patients with the reduced dose of 2.5 mg/d.

Moreover, the risk of bias in clinical studies, including those by Beal (1995) and Struwe (1993), has been critically reviewed[13].

The study by Ballard and de Wit[14] has the disadvantage that it was conducted on a very small patient collective and has not yet been reproduced. An experimental flaw is that the effects of other drugs taken by the trial persons could not be excluded, and that the placebo drink administered with THC also contained alcohol. This small trial is the only one used by EFSA to derive a HBGV that describes very small effects of THC on subjective well-being and responsiveness at a dose of 2.5 mg/d in healthy adults:
"When given alone, 2.5 mg THC produced modest effects on subjective ratings, measures of cognitive performance, and physiological measures. Although participants did not report

[12] M. Struwe, S. H. Kaempfer et al., Effect of dronabinol on nutritional status in HIV infection, July 1993, Annals of Pharmacotherapy 27(7-8):827-31
[13] Kleijnen Systematic Reviews Ltd, Systematic review of Cannabis for Medical Use, September 2014, York (UK)
[14] Ballard et al., Combined effect of acute, very-low-dose ethanol and delta9-tetrahydrocannabinol in healthy human volunteers, Pharmacol. Biochem. Behav. (2011); 97(4): 627-631.

feeling any drug effects, THC significantly reduced POMS 'vigor' scale scores and increased sedation ..."

It may even be questioned if effects on "mood state" or slight sedation are relevant endpoints for deriving a HBGV for THC. Summarising the result, the author's state: „... *these very-low doses of ethanol and THC had only moderate effects on isolated measures...*"

However, another study did not come to the same conclusion for this dose[15]: No THC effect was found at a dose of 2.5 mg/d; only at elevated doses of 5 or 10 mg/d changes were reported in subjective well-being (previous cannabis use could not be ruled out).

A recent Israeli study by Bar-Sela et al.[16] found no significant side effects of a combination of 4.75 mg of THC and 0.25 mg of CBD daily for periods ranging from 2 weeks to 6 months for 10 patients in cancer therapy.

Summarising, instead of relying on very few inconclusive studies for a HBGV derivation, EFSA's scientific committee is asked to take into account the ensemble of scientific studies on the effects of THC of meanwhile more than fifty years (since elucidation of the chemical structure of THC by Mechoulam in 1964[17], and the investigation of its properties and effects as an isolated compound as well as its interaction with other substances)[18].

Results of many other human studies on THC also do not indicate adverse effects at a dose of 2.5 mg/d, or the studies have only been done at doses of at least 5 mg/d in order to observe at least any significant effects (e.g. Petro & Ellenberger 1981[19], Chesher[20] 1990, Leson et al. 2001[21], Strasser 2006[22] , and Review by Zuurman 2009[23]).

For example, Petro and co-workers (cit. lit.) report: "*Side effects of the 5- or 10-mg oral dosage were minimal. One patient reported feeling "high" after 10 mg, and another reported a "high" after placebo. No other patients reported side effects at the relatively low doses we used.*"

In the study by Strasser et al. (2006) it is reported in the summary of results:
"*Intent-to- treat analysis showed no significant differences between the three arms [cannabis extract, THC, or placebo] for appetite, QOL [quality of life], or cannabinoid-related toxicity.*"

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[15] Gray, K. M. et al.: Δ9-Tetrahydrocannabinol in Older Adolescents with Marijuana Use Disorders, Pharmacol Biochem Behav. 2008; 91: 67-70. doi:10.1016/j.pbb.2008.06.011.
[16] Bar-Sela et al., https://doi.org/10.1177/1534735419881498, The Effects of Dosage-Controlled Cannabis Capsules on Cancer-Related Cachexia and Anorexia Syndrome in Advanced Cancer Patients: Pilot Study, Integrated Cancer Therapies 18, 1-8 (2019).
[17] Y. Gaoni, R. Mechoulam: *Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish*. In: *Journal of the American Chemical Society*. 86, 1964, S. 1646–1647, doi:10.1021/ja01062a046.
[18] https://de.wikipedia.org/wiki/Raphael_Mechoulam (accessed 21.09.2020)
[19] Petro, D. J. et al.: TREATMENT OF HUMAN SPASTICITY WITH DELTA-9-TETRAHYDROCANNABINOL, J. Clin. Pharmacol. 1981; 21: 413S--416S
[20] Chesher, G. B. et al. : The Effects of Orally Administered A9-Tetrahydrocannabinol in Man on Mood and Performance Measures: A Dose-Response Study, Pharmacology Biochemistry & Behavior. Vol. 35, pp. 861-864 (1990).
[21] Leson, G., Pless, P., Grotenhermen, F., Kalant, H., ElSohly, M. A., Evaluating the Impact of Hemp Food Consumption on Workplace Drug Tests; J. Analyt. Toxicol. 25(2001): 691-698.
[22] Strasser et al., Comparison of Orally Administered Cannabis Extract and Delta-9-Tetrahydrocannabinol in Treating Patients With Cancer-Related Anorexia-Cachexia Syndrome: A Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial From the Cannabis-InCachexia-Study-Group, J. Clin. Oncol. 24(21), 3394-3400.
[23] Zuurman, L. et al.: Biomarkers for the effects of cannabis and THC in healthy volunteers, Brit. J. Clin. Pharmacol. 67:1, 5-21 (2008), DOI:10.1111/j.1365-2125.2008.03329.x

The Verum group had received 2.5 mg of THC twice daily, and only in case of adverse effects, this dose was reduced for some patients to 2.5 mg/d once.

The review by Zuurman et al. includes studies with oral administration of THC – and although not differentiating the tabulated effects by administration routes – only mentions adverse effects of THC at substantially lower doses than 7 mg/d for pulmonary administration, and not for oral administration (and only the latter is relevant for a toxicological assessment of THC in food).

Grotenhermen et al.[24] had set up a comprehensive assessment of the risks of THC intake to human health. They conclude on the LOAEL and NOAEL for THC:
"Acute effects: The lowest observed adverse effect level (LOAEL) for the ingestion of THC, representing a slight impairment in psychomotor functions, is represented by a single dose of 5 mg of oral THC. The NOAEL for psychotropic effects caused by the oral ingestion of THC has been established at 5 mg/day."
The authors derive an ADI (Acceptable Daily Intake) of 500 µg of THC/d for an average adult with an overall uncertainty factor of 20 because even at 10 mg of THC per day there is no cumulative effect.

Also later, in 2007, Grotenhermen[25] states:
"With inhalation, the threshold for psychological effects is lower (a single dose of ca. 2 – 3 mg of THC) compared to oral intake (a single dose of usually ca. 5 – 20 mg of THC) [26]"

A more recent study from 2017 on gender differences in the subjective perception of oral THC in cannabis users[27] was only able to identify adverse effects at a dose of 5 mg/d.

The lesson is clear: the evidence for adverse effects of THC at an oral dose of only 2.5 mg/d is marginal. In fact, most of the studies cited here point to a LOAEL of 5 mg/d.

For this reason, the health authority for Australia and New Zealand (FSANZ) has also derived a dose of 5 mg THC per day as LOAEL in a re-examination (2011)[28] of its careful and comprehensive risk assessment of THC in food, from which it has confirmed a level of 6 µg THC/kg bw as HBGV, basing - inter alia - on the comprehensive work by Chesher (cit. lit.).

In 1996, the Swiss Federal Office of Public Health (SFOPH) had derived a HBGV of 7 µg/kg bw on the basis of various studies[29], also using a LOAEL of 5 mg/d of THC per adult person, including the calculation of plasma and urine concentrations to detect possible cannabis abuse and to distinguish it from harmless THC ingestion through food. Croatia is also an EU

[24] Grotenhermen, F., Leson, G., Pless, P., ASSESSMENT OF EXPOSURE TO AND HUMAN HEALTH RISK FROM THC AND OTHER CANNABINOIDS IN HEMP FOODS, Oct 11 (2001), Leson Environmental Consulting, Berkeley, CA.
[25] Grotenhermen, F., The toxicology of cannabis and cannabis prohibition. Chem Biodivers 2007;4(8):1744-69.
[26] Hagenbach et al., The treatment of spasticity with Delta9-tetrahydrocannabinol in persons with spinal cord injury. Spinal Cord. 2007 Aug;45(8):551-62.
[27] Fogel, J. S. et al., Δ9-THC in cannabis users, Pharmacol. Biochem. Behav. 2017 Jan; 152:44-51.
[28] Food Standards Australia New Zealand, Supporting Document 1, Risk Assessment Report, Application A360 (2011).
[29] Bundesamt für Gesundheitswesen (BAG), Bulletin 24, 24.6.1996, Lebensmittel-Info: Verwendung von Hanf in Lebensmitteln und Gebrauchsgegenständen, Kreisschreiben Nr. 2 of 13.3.1996.

country with an up-to-date HBGV at the higher level which is based on sound scientific reasoning[30].

As can be seen, in the assessment by other state authorities the maximum daily intake values for THC are much higher than in Germany or EU.

A "meta-study" from the USA by Kruger and Lodder[31] is a very short communication that does not present any data at all which would allow the derivation of a TDI. The TDI of 1.5 µg THC/kg bw proposed by the authors is not comprehensible at all. Furthermore, a meta-analysis cannot generate more experimental data on the toxicology of THC than those generated in original studies. The parameter "change in heart rate", which is mentioned as important, is not specific for THC, and the study on Namisol® by Klumpers et al.[32] cited there reports a dose of 6.5 or 8 mg/d THC orally and not of 2.5 mg/d.

In general, caution should be exercised when citing details of dose-response relationships from reviews or meta-studies, as certain effects are often not correctly reported for a specific dose. This can only be demonstrated with a concrete example: in reviews[3334] of Nadulski's study[35], a dose of 10 mg/d orally was used instead of 2.5 mg THC as reported in the reviews. If you only rely on secondary literature, you might be tempted to draw the wrong conclusions. Other studies (cited above), including larger human clinical trials using THC for therapeutic purposes in patients, have observed adverse effects on the CNS only at a daily dose of 5 mg THC and therefore suggest a LOAEL of 5 mg THC/d, corresponding to 71 to 83 µg/kg body weight[36].

The effects of 2.5 mg of pure THC on the central nervous system could be a slight effect on psyche (mood alteration) in sensitive individuals. The effects are transient and reversible and less than the effects of drinking alcohol, for example, after drinking a 0.33-litre bottle of beer (containing 5% alcohol by volume). To date, however, no adverse effects or even health impairments have been found below a daily intake of 2.5 mg THC per adult.

[30] Hrvatska Agencija za Hranu, Znanstveno Mišljenje, Znanstveno mišljenjeo Utjecaju na zdravljerazličitih vrsta hrane od sjemenki koja sadržisjemenke industrijske konoplje, Radna grupa za donošenjeznanstvenog mišljenja (Zahtjev HAH-Z-2015-1) 25. svibnja 2015.

[31] Kruger, C., Lodder, R., Establishing limits for THC-content in hemp-derived foods, Food Technol. 72, 20-21 (2018).

[32] Klumpers et al.: Novel Δ⁹-tetrahydrocannabinol formulation Namisol® has beneficial pharmacokinetics and promising pharmacodynamics effects, Br. J. Clin. Pharmacol. 74:1, 42–53.

[33] Badowski, M., Perez, S. E., Clinical utility of dronabinol in the treatment of weight loss associated with HIV and AIDS, HIV/AIDS-Research and Palliative Care 2016:8, 37-45

[34] Badowski, M. E., A review of oral cannabinoids and medical marijuana for the treatment of chemotherapy-induced nausea and vomiting: a focus on pharmacokinetic variability and pharmacodynamics, Cancer. Chemother. Pharmacol. (2017)80:441-449.

[35] Nadulski et al., Simultaneous and sensitive analysis of THC, 11-OH-THC, THC-COOH, CBD, and CBN by GC-MS in plasma after oral application of small doses of THC and cannabis extract, J. Anal. Toxicol., Nov-Dec 2005;29(8):782-9. doi: 10.1093/jat/29.8.782.

[36] In Germany, the BgVV (now BfR) calculated an average adult body weight of 60 kg, in the EU the EFSA calculated an average adult body weight of 70 kg. See also: Grotenhermen et al.: cit. lit.

2. Critical review of the application of uncertainty factors for derivation of a HBGV from the LOAEL/NOAEL and for THC limits in food

Currently, on the European level, and in most EU Member States, there are no legally binding daily maximum levels for THC in food or in food supplements, only non-binding recommendations. As mentioned, in Germany, today's BfR, in 1997, recommended a maximum daily intake of 1-2 µg of total-THC per kilogram body weight as part of precautionary consumer and health protection, taking into account an overall safety factor of 20-40 applied to the LOAEL. Possible interactions with alcohol or drugs have already been included. On the basis of this maximum daily intake, recommendations on guideline values for THC in food were issued in Germany.

At that time, food supplements were not yet assessed by BgVV/BfR with regard to the guideline values for THC in ready-to-eat foods. This is because the term "food supplements" was only legally defined in 2002 (EU Directive 2002/46/EC). Since then the daily intake of possibly "active" substances is limited in the case of supplements by the recommended intake on the label of the respective product.

We consider the above-mentioned safety factors of 20 - 40 to be highly questionable and incomprehensible. In its risk assessment, EFSA concludes[37] *"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."* Therefore, in the derivation of a HBGV it is not justified to apply the standard uncertainty factor of 10 for the intraspecies variability because this factor should be applied only if the adverse effect was observed as a common one to most of the trial persons in a representative human study and if it was of statistical significance. However, the latter was not the case in the cited studies.

Moreover, lower uncertainty factors are to be applied if the observed effects (LOAEL) are mild and transient. Grotenhermen et al.[38] state:
"When using a LOAEL for determination of the sub-threshold dose, the severity of the effect at the LOAEL level is to be considered. Mild effects that may represent an adverse impact will require lower UFs. Previous reviews of LOAEL/NOAEL for a range of toxic chemicals indicate that corresponding uncertainty factors mostly range between 1 and 6 (Dourson et al. 1996[39])."

Instead, a much lower overall uncertainty factor of 6, for example, would have been appropriate in this case, starting with an assumed LOAEL of 2.5 mg/d of THC, thus giving a HBGV of >400 µg per adult and day.

[37] EFSA Scientific Opinion (2015), p. 65, 2nd paragraph, last sentence.
[38] Grotenhermen, F., Leson, G., Pless, P., ASSESSMENT OF EXPOSURE TO AND HUMAN HEALTH RISK FROM THC AND OTHER CANNABINOIDS IN HEMP FOODS, Oct 11 (2001), Leson Environmental Consulting, Berkeley, CA.
[39] Dourson et al., Evolution of Science-Based Uncertainty Factors in Noncancer Risk Assessment, REG. TOXICOL. PHARMACOL. 24. 108-120 (1996), Article No.0116.

Compared to other substances whose content in food or beverages must be limited (e.g. caffeine, nicotine, alcohol, morphine), the approach of these extremely high safety factors for THC is highly questionable[40] [41].

Coffee and alcohol have been shown to have a much stronger effect on the central nervous system in socially tolerated quantities. With coffee, a daily consumption of four cups would have to be regulated if the analogous approach were used. In the case of alcohol, on the other hand, an analogous limitation would consequently lead to a restriction of the marketability of dairy products such as yoghurt, fruit juices and the like (because of "grain alcohol", alcohol produced by fermentation) and to a ban on the marketing of all larger containers of alcoholic beverages and the high-proof alcoholic beverages (which are on the market up to a content of 80% alcohol, e.g. "straw rum" in Austria).

We would like to point out that THC is not a cell poison, given its potential health risk compared to alcohol.

To date, there is no scientific evidence that, for example, THC consumption of 7 µg/kg body weight is no longer "safe" or that it can be assumed to pose a health risk or unacceptable damage to health. Accordingly, as mentioned, the Swiss Federal Office of Public Health (BAG) had already set a TDI value of 7 µg/kg bw for Δ9-THC in 1996.

In a study by Leson et al (2001)[42], subjects were given different amounts of THC in a mixture of hemp oil and rapeseed oil over a period of 10 days. The THC doses ranged from 90 µg/d to 600 µg/d. In the study, no psychotropic side effects were observed in the volunteers, a fact which was confirmed by the author[43].

And in other countries such as Croatia, Australia and New Zealand, the TDI for THC is 7 µg/kg bw and 6 µg/kg bw (bw: body weight) respectively.

If one also compares the safety assessment of THC with other actually dangerous substances such as opium alkaloids, it can be seen, particularly in the case of opium alkaloids, that the BfR has given morphine a safety factor of only "5" (!) (which led to an ARfD of 6.3 µg morphine (equivalent)/kg bw), while EFSA (2011 and 2018) assumed a safety factor of only "3" [Note: In studies with this dose, the placebo group also shows some effects like the Verum group], from which an ARfD of 10 µg morphine (equivalent)/kg bw was derived. It should be noted that the effective dose of opium alkaloids leads to pain relief and sedation, similar to THC. If, on the other hand, the same procedure with the "uncertainty factor 5" was applied to the derivation of an ARfD for THC, an ARfD of approx. 7 µg THC/kg bw (*from 2,500 µg single dose, divided by factor 5 and related to 70 kg body weight*) would be obtained. This corresponds exactly to the value proposed by EIHA.

[40] Iffland et al., Comparison of EFSA's rationale behind using uncertainty factors for plant ingredients in food, EIHA Paper, Hürth (2016), www.eiha.org.
[41] Banas et al.: Reasonable guidance values for THC (Tetrahydrocannabinol) in food products. Position Paper of the European Industrial Hemp Association (EIHA), Hürth, Germany (2017).
[42] Leson, G., Pless, P., Grotenhermen, F., Kalant, H., ElSohly, M. A., Evaluating the Impact of Hemp Food Consumption on Workplace Drug Tests; J. Analyt. Toxicol. 25(2001): 691-698.
[43] Personal communication by one of the authors to Beitzke, B.

3. Conclusions

In the view of the low HBGV and the further derived maximum THC levels for food, it is not surprising that in 2018 the German BfR issued a report on THC contents in food regarded too high. This report has already been critically reviewed because of lacking differentiation between psychoactive delta9-THC and THCA, the latter being the non-psychoactive component of so-called total-THC.[44], and - inter alia - because of insufficient evidence of data from chemical analysis.

It is appreciated here that EFSA has been much more diligent and careful in its recent assessment of acute human exposure to THC because it acknowledged the difficulties with correct chemical analysis of delta9-THC-contents in food, although it continues to base its risk assessment on delta9-THC on the extremely low HBGV of 1 µg/kg bw.

Exceeding the current guideline values for THC in food is certainly not related to improper or even insufficient cleaning of hemp seeds by manufacturers prior to food production, but is due to the unrealistic and unnecessarily strict guideline values themselves.

Based on scientific reasoning a daily intake of up to 7 µg THC per kg body weight by food consumption can be judged as safe for the consumer.

Authors:
Dr. rer. nat. Bernhard Beitzke, Independent Scientific Consultant and Member of the EIHA Advisory Committee
Co-Author: Daniel Kruse, EIHA President and hemp food operator (trade since 1995, production since 2002)

[44] Skoczinski et al.: Limit and guideline values for THC (tetrahydrocannabinol) in hemp foods, nova Institut für Ökologie und Innovation, Hürth (May 2019), http://news.bio-based.eu/limit-and-guideline-values-for-thc-tetrahydrocannabinol-in-hemp-foods/