Limit and guideline values for THC (tetrahydrocannabinol) in hemp foods

Analysis and evaluation of the opinion of the German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR) from 8 November 2018 "Tetrahydrocannabinol levels are too high in many hemp-containing foods – health impairments are possible" No. 034/2018.

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nova-Institute

nova-Institute was founded as a private and independent institute in 1994 and is located in the chemical park Knapsack in Hürth. For more than 20 years, the nova-Institute has been researching and consulting worldwide with a focus on bio-based and CO₂-based economics in the areas of food and feed, pharma as well as bio-based chemistry and polymers. In the field of the pharmaceutical and biotechnological use of cannabis, the nova-Institute offers among other things scientific assessments of the pharmaceutical effects of CBD and THC, advice on regulatory issues and technology scouting for the biotechnological production of cannabinoids.

The content includes scientific evaluations, techno-economic evaluations, markets, sustainability, marketing support, B2B communication as well as policy and strategy. Each year, nova organizes several large conferences on these topics, nova employs 30 people and has an annual turnover of approximately 3 million euros.
Evaluation of limit and guideline values of THC (tetrahydrocannabinol) in hemp foods

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Daniel Kruse, a pioneer in the hemp industry for 26 years, is founder and managing director of Hempro International GmbH & Co. KG and HempConsult GmbH, two of the leading hemp companies in Europe. Founded in 2002, Hempro International is one of the first and largest manufacturers of hemp food and produces raw materials such as peeled hemp seeds, hemp oil and hemp protein.

By consistently implementing a strategy focused on product quality, Hempro International has succeeded in becoming one of the largest suppliers in the European hemp industry. Based on a strong global network, HempConsult (founded in 2012) not only follows industry trends and developments in the international hemp markets, but also offers support to companies and stakeholders in the industry in the development of strategic goals and their successful and sustainable implementation.

Since 2013 Daniel Kruse has been a member of the board of the European Industrial Hemp Association (EIHA) and in this function brings in his profound knowledge of cannabinoids (e.g. THC/CBD) in food. Kruse represents the interest groups of the hemp industry before the European Union and the German government, where his work has helped to improve the legal and regulatory framework for the hemp industry.
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Background and Summary

Hemp foods containing different components of the hemp plant in their original or processed form are enjoying increasing popularity worldwide. In North America, China and also Europe hundreds of hemp products are on the market and, with their valuable fatty acids and proteins, belong to the trend products of a healthy nutrition.

Since small amounts of the psychoactive tetrahydrocannabinol (Δ9-THC), hereinafter briefly referred to as THC, remain in the food even after the most careful processing, limit or guideline values must be defined that reliably protect the consumers from side effects. As we present in this study, a number of countries such as Australia, Canada and Switzerland have set themselves similar limit or guideline values. These allow producers sufficient leeway to supply consumers with a variety of hemp products while avoiding any side effects from THC. More than ten years of experience in Canada confirm this.

The legal situation in Europe is more complicated and constitutes an obstacle to the further development of the industry. In Europe, there are no uniform limit or guideline values for residual THC contents in food, not even uniform guideline values for consumption. Back in 1997, the German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR) (formerly BgVV) established THC guideline values that, until today, represent the strictest international values and have been criticised by experts for years as being too restrictive. When the Federal Ministry of Food and Agriculture (Bundesministerium für Ernährung und Landwirtschaft, BMEL) commissioned the BfR to clarify some fundamental aspects regarding the assessment of the THC content in food at the request of the monitoring authority of a federal state, many scientists and producers hoped for a comprehensive reassessment and adaptation as well as international harmonisation of the guideline values.

These hopes were severely disappointed by the BfR opinion No. 034/2018 from 8 November 2018 "Tetrahydrocannabinol levels are too high in many hemp-containing foods – health impairments are possible". Instead of a comprehensive reassessment, 40 pages explain why the 1997 established THC guideline values would continue to apply and that, if they were to be amended, they would rather be tightened than loosened. Germany would thus create clear barriers to the growing hemp industry and make it more difficult for the population to access hemp products as a result of higher prices.

In this situation the European Industrial Hemp Association (www.eiha.org), the industry association of the European hemp industry, asked the independent nova-Institute to analyse and evaluate the BfR statement. In cooperation with representatives of the scientific advisory board and the executive committee of the association, a 29-page-long evaluation was created. In the following, the most important results of this evaluation will be summarised.

In the opinion of the scientists, the BfR has taken the easy way out with its statement and defence of its recommendations from 1997. Much has happened since 1997, new scientific findings have been gained and comprehensive experiences with hemp foods have been made in many countries – both have not been adequately considered. Six important scientific studies published after the year 2000 and the detailed EIHA position paper “Reasonable guidance values for THC (tetrahydrocannabinol) in food products” (September 2017) were not regarded when reviewing their own risk assessment; they were simply ignored, even though they were known to the BfR. If the new scientific findings were to be considered, a defence of the old guideline values would fall short. It becomes apparent that a comprehensive revision of the recommendations is necessary and that the THC guideline values can be significantly increased without any risk when consuming hemp products - and internationally harmonised.
In order to establish guideline values with a sufficient safety distance to undesirable effects, one must know the LOAEL (lowest observed adverse effect level) or the NOAEL (no observed adverse effect level) and then apply a factor that takes into account the different sensitivities of the consumers. The European Food Safety Authority (EFSA) has issued clear recommendations on the methodological approach.

**Uncertainty factor**

The BfR applies an uncertainty factor of 20-40 to THC, since no NOAEL is known for THC. Therefore, in addition to the usual EFSA uncertainty factor of 10, the BfR uses a further uncertainty factor of 2-4 for interindividual differences, namely for the extrapolation from the known LOAEL of THC to NOAEL. But according to current scientific knowledge, this is no longer tenable. Due to the more recent clinical experience on active THC, we know today where the NOAEL lies for the large majority of patients. An additional factor of 2-4 is therefore no longer justifiable. Also, the reasoning that there is no sufficient data available on the effects of THC appears to be not very reliable because in the current evaluation of THC twice as many studies are used as in the evaluation of nicotine. In addition, today numerous other studies exist that further support a more differentiated evaluation of THC. If one compares the uncertainty factor of 20-40 with the uncertainty factors the BfR assigns to other psychologically active substances, the procedure and justification does no longer appear scientifically comprehensible.
### Evaluation of THC in hemp foods

<table>
<thead>
<tr>
<th>Substance</th>
<th>Adverse effects</th>
<th>Uncertainty factor by BfR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>effects on the central nervous system: euphoria, clouding of consciousness, impairment of cognitive abilities and judgement, reduced driving ability and ability to operate machines, aggressiveness, nausea, vomiting, habituation, addiction, addiction, withdrawal symptoms (irritability, dysphoria)</td>
<td>–</td>
</tr>
<tr>
<td>Caffeine</td>
<td>effects on the central nervous system: restlessness, irritability, nervousness, tremors, insomnia, anxiety, habituation, dependence, addiction, withdrawal symptoms (irritability, dysphoria) effects on the vegetative nervous system: increase of heart rate, arrhythmias, vasoconstrictor in the brain, vasodilator in the periphery</td>
<td>–</td>
</tr>
<tr>
<td>Nicotine</td>
<td>effects on the central nervous system: dizziness, habituation, dependence, addiction, withdrawal symptoms (irritability, dysphoria) effects on the vegetative nervous system: stimulating, increase in salivary flow, increase in heart rate and blood pressure, narrowing of peripheral blood vessels</td>
<td>4.4</td>
</tr>
<tr>
<td>Opium alkaloids (morphine and codeine)</td>
<td>effects on the central nervous system: nausea, vomiting, loss of appetite, constipation, sedation, drowsiness, mood changes, euphoria, miosis; Respiratory depression and constipation, changes in the hormonal and autonomic nervous systems.</td>
<td>5</td>
</tr>
<tr>
<td>(\Delta^2)-THC</td>
<td>effects on the central nervous system: mood swings, fatigue, dizziness, loss of consciousness, insomnia, nausea, euphoria, habituation, dependence, addiction, withdrawal symptoms; effects on the vegetative nervous system: increased heart rate, changes in blood pressure</td>
<td>20-40</td>
</tr>
</tbody>
</table>

For nicotine, opium alkaloids, but especially for caffeine and alcohol, very low (or no) uncertainty factors are applied, even lower than the recommended standard uncertainty factor of 10 for interindividual differences. For THC, on the other hand, a strict methodology is followed and then further exacerbated by applying an extra factor on top, which is not scientifically tenable. If, for example, the BfR were to apply comparable standards to alcohol as to THC, bread or orange juice would no longer be marketable. And similarly, there would be no more poppy-seed cakes or poppy-seed rolls to purchase if opium alkaloids were subject to the same procedure for risk assessment as THC.

The BfR risk assessments for the substances mentioned are inconsistent, inscrutable and hardly comprehensible. This systematic unequal treatment of substances with similar effects will not withstand an overarching risk assessment and is scientifically outdated.

### Active THC and patients

There are further errors and inconsistencies in the BfR statement that systematically overestimate THC risks: The studies used by the BfR only use active THC, whereas in reality THC always occurs together with other cannabinoids that can influence the effect of active THC. In addition, all studies
used were medical studies and therefore conducted exclusively on patients, sick persons, who are usually more sensitive than healthy people.
But when assessing "health claims" on food, the EU Commission usually only considers studies that were carried out on healthy volunteers. Clinical studies on sick volunteers generally have the disadvantage that possibly relevant physiological parameters of the volunteers are altered. This scientific principle must of course be observed not only in health-related effects, but also in risk assessment.

**Total THC and active THC**

The biggest error, however, results from the imprecise distinction between total THC and the active form of THC ($\Delta^9$-THC). In most hemp foods, THC is primarily present in its non-active form (up to 90%), which only converts into its active form after prolonged heating. A complete transformation is almost impossible under normal production and preparation conditions of food.

If the guideline values refer to total THC and not only to the active form, the guideline values are systematically set too strict. In other words, the BfR derives much too high active THC contents in food in its approach. This leads to objectively inaccurate results and scientifically completely wrong conclusions for the risk evaluation of THC.

**Bottom line**

The BfR has once again missed the opportunity to comprehensively revise the THC guideline values, to take account of current scientific findings and to harmonise the German THC guideline values internationally. The attempt to defend the old recommendations fails because the arguments are based on outdated information, systematically ignoring studies and findings from the last 18 years for a differentiated risk assessment. The lack of a clear distinction between total THC and active THC, which has long been the scientific standard, is also a weak point of the BfR statement that cannot be ignored.

Why the BfR shows such, scientifically not justifiable, severity with the THC in food, while the reference values for comparable substances such as alcohol, caffeine, nicotine and opium alkaloids are disproportionately indulgent and generous, can at this point only be speculated. Are there lobby interests behind this? Shall competition for established products on the market be prevented? Or is it still a remnant of the fight against the alleged "devil drug cannabis"?

Whatever the reason, there can be no speculation about the following conclusion: The measurements and methodologies of the BfR are so different that they cannot prevail. The current risk assessment of THC by the BfR is inadequate according to current scientific knowledge, goes against international experiences and potential harmonisation, and should therefore be urgently revised.
**Procedure**

The published opinion of the BfR "Tetrahydrocannabinol contents are too high in many hemp-containing foods - health impairments are possible" (No. 034/2018 of BfR from 8 November 2018) (BfR 2018a) deals with the tetrahydrocannabinol (THC)-content in hemp-containing foods and finds them currently as too high. In addition to this, the values for the tolerable daily intake (TDI) determined by the former BgVV in 1997 (BgVV 1997) and 2000 (BgVV 2000) as well as by EFSA in 2015 (EFSA 2015a), setting the basis for the limit values of THC content in food, were confirmed.

The following study contains a systematic, scientific analysis of the BfR's approach towards its definition and determination of limits and guideline values for THC intake and content in hemp-containing foods.

The study first shows that the determination, justification and confirmation of the limit values for the daily intake of THC by the BfR is already based on only conditionally suitable scientific studies, a much too superficial consideration of the available scientific evidence and an inconsistent approach in the risk assessment of THC (see chapter 1).

In addition, it is shown that the limit values for daily THC intake, derived from the abovementioned guideline values, and the determination of the THC contents in food confirm the scientific inadequacies previously indicated, since again the actually present THC form in the hemp food and its possible transformation under certain circumstances is not considered and weighted in the scientifically required and expected differentiation (see chapter 2).

### 1 Determination of the tolerable daily intake of $\Delta^9$-THC

Different, country-specific / region-specific authorities or institutions are generally responsible for the risk assessment of different substances or food ingredients. Not for every substance there is a risk assessment in every country, and the procedure for a risk assessment does not follow general standards, neither in different institutions nor within a single authority. Table 1 shows the risk assessment of THC in several countries and regions by different institutions. These are based on different studies and apply the criteria in varying ways, e.g. uncertainty factors for THC and opium alkaloids (1.1; Table 2; Table 3). It should be noted that active THC is hereinafter referred to as phenolic $\Delta^9$-THC and refers only to pure $\Delta^9$-THC without its non-active precursor $\Delta^9$-THC-A-A (for details see 1.4).

In the following, various points of criticism will be analysed and explained, which highlight the scientific shortcomings in the BfR statement '"Tetrahydrocannabinol contents are too high in many hemp-containing foods - health impairments are possible" (No. 034/2018 of BfR from 8 November 2018) (BfR 2018a). Furthermore, approaches for a redefinition based on a more holistic scientific view will be provided.
Evaluation of limit and guideline values of THC (tetrahydrocannabinol) in hemp foods

Table 1: Risk assessment of tetrahydrocannabinol (THC) from different institutions. Listed are the respective institution, the year of the risk assessment, the uncertainty factor applied, the factors considered, the most sensitive point of action, the type of study on which the risk assessment is based, the type of THC used and the derived tolerable daily intake (TDI) per kg body weight, as well as the resulting guideline and limit values of the total $\Delta^9$-THC content in food (ppm).

UF: Uncertainty factor, * at that time still Federal Institute for Health Consumer Protection and Veterinary Medicine (Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin, BgVV), # in hemp seed-based feed.

<table>
<thead>
<tr>
<th>Institution</th>
<th>Year (renewed assessment)</th>
<th>Country / region</th>
<th>UF</th>
<th>Consideration</th>
<th>Most sensitive point of action</th>
<th>Underlying study type</th>
<th>Form of THC used in the study</th>
<th>TDI / ARfD ($\Delta^9$-THC mg/kg bw or total $\Delta^9$-THC mg/kg bw*)</th>
<th>Limit values for $\Delta^9$-THC or total $\Delta^9$-THC content in food (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bundesamt für Gesundheit (BAG) (BAG 1996)</td>
<td>1995</td>
<td>Switzerland</td>
<td>10</td>
<td>accumulation of $\Delta^9$-THC in the body</td>
<td>psychotropic effects</td>
<td>administration of oral doses of 5 and 20 mg/person</td>
<td>phenolic $\Delta^9$-THC (dronabinol)</td>
<td>0.007</td>
<td>0.2-20</td>
</tr>
<tr>
<td>Bundesinstitut für Risikobewertung (BfR) (BgVV 1997, 2000) (BfR 2018a)</td>
<td>1997* (2000; 2018)</td>
<td>Germany</td>
<td>20-40</td>
<td>various scientific uncertainties</td>
<td>effects on the central nervous system (dizziness, disturbances of consciousness, insomnia, nausea, Euphory, anxiety) and increase of heart rate</td>
<td>administration of oral doses to healthy (Ballard and de Wit 2011) and ill test persons (Beal et al. 1995; Beal et al. 1997; Struwe et al. 1993)</td>
<td>phenolic $\Delta^9$-THC (dronabinol)</td>
<td>0.001-0.002</td>
<td>0.005-5</td>
</tr>
<tr>
<td>Food Standards Australia New Zealand (FSANZ) (FSANZ 2002, 2012)</td>
<td>2002 (2012)</td>
<td>Australia, New Zealand</td>
<td>10</td>
<td>interindividual differences</td>
<td>effects on the central nervous system (influence on movement)</td>
<td>administration of oral doses to healthy test persons (Chesher et al. 1990)</td>
<td>phenolic $\Delta^9$-THC (dronabinol)</td>
<td>0.006</td>
<td>0.27-34</td>
</tr>
</tbody>
</table>
### Evaluation of limit and guideline values of THC (tetrahydrocannabinol) in hemp foods

| Authority/Agency | Country | Year | UF | Interindividual differences | Extrapolation from LOAEL to NOAEL | Effects on the central nervous system (dizziness, disturbances of consciousness, insomnia, nausea, Euphory, anxiety) and increase of heart rate | Administration of oral doses to healthy test persons (Chesher et al. 1990) and ill (Beal et al. 1995; Beal et al. 1997; Petro and Ellenberger 1981; Strasser et al. 2006; Zajicek et al. 2003; Zajicek et al. 2005) test persons | Phenolic Δ⁹-THC (dronabinol), total Δ⁹-THC and other cannabinoids (cannabis extract) | Total Δ⁹-THC (hemp oil) | Not determined |
|------------------|---------|------|----|-------------------------------|-----------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------|
| European Food Safety Authority (EFSA) (EFSA 2015a) | Europe | 2015 | 30 | UF 10 interindividual differences | UF 3 extrapolation from LOAEL to NOAEL | effects on the central nervous system (dizziness, disturbances of consciousness, insomnia, nausea, Euphory, anxiety) and increase of heart rate | administration of oral doses to ill test persons (Beal et al. 1997) and meta-analysis of car accidents and usage of cannabis (Ramaekers et al. 2004) | phenolic Δ⁹-THC (dronabinol); Cannabis | 0.001 | not determined |
| Croatian Food Agency (HAH) (HAH 2011) | Croatia | 2015 | 20 | UF 10 interindividual differences | UF 2 extrapolation from LOAEL to NOAEL | effects on the central nervous system (influence on movement) | administration of oral doses to healthy test persons (Geiwitz and Ad Hoc Committee on Hemp Risks 2001; Grotenhermen et al. 2001) | Total Δ⁹-THC (hemp oil) | 0.007# | 2-20 |
| European Industrial Hemp Association (EIHA) (Baňas et al. 2017) | Germany, Europe | 2017 | 10 | Interindividual differences | | effects on the central nervous system (influence on movement) | administration of oral doses to healthy test persons | phenolic Δ⁹-THC (dronabinol), total Δ⁹-THC and other cannabinoids (cannabis extract) | 0.007 | 0.02-10 |
| Health Canada (Geiwitz and Ad Hoc Committee on Hemp Risks 2001) | Canada | – | 10 | Interindividual differences | | ”psychoactive and harmful effects“ | See bibliography in (Geiwitz and Ad Hoc Committee on Hemp Risks 2001) | Phenolic Δ⁹-THC (dronabinol), total Δ⁹-THC and other cannabinoids (cannabis extract) | 0.014 | up to 10 |
1.1 Uncertainty factors of other substances compared to THC

Due to the different ways of looking at and investigating the effects of THC, the associated scientific uncertainties and the lack of a uniform standard procedure for the risk assessment of substances and food ingredients, it can be stated that both the BfR and EFSA – compared to the study results - unnecessarily demand a much too high uncertainty factor of 30 in their risk assessments of THC. As a result, this establishes a very low tolerable daily intake (TDI) of 0.001 mg Δ^9-THC/kg bw. In their risk assessments BfR and EFSA do not consider the studies explained below (Table 2).

In view of this objectively incomprehensible strictness on THC limit values, the question also arises as to why there are no such risk assessments or limit values for other substances acting on the nervous system, such as alcohol or caffeine, or why these are disproportionately lenient as in the case of opium alkaloids (Table 2; Table 3).

The authors of this study are not alone in their evaluation of the different risk assessments of critical substances in food. The margin of exposure methodology was used to show that the risk of cannabis (and thus Δ^9-THC) turns out to be far lower than the risks of alcohol (highest), nicotine and opiates (Lachenmeier and Rehm 2015).

Alcohol

As already described in detail in 2016 (Iffland et al. 2016) there is no risk assessment for alcohol by the BfR or the EFSA, although the LOAEL (lowest observed adverse effect level) is 10 g/day (for women) (Burger et al. 2004; Seitz and Bühringer 2010), which leads to a TDI of 1 g/day assuming an uncertainty factor of 10 for interindividual differences. However, this value of 1 g/day would already be reached with the consumption of two bread rolls and a glass of orange juice for breakfast. Because the alcohol content in food, such as rolls and fruit juices, is actually much higher than you might think: 1.2 g alcohol is contained per 100 g rolls, which corresponds to about three rolls. One litre of orange juice contains 0.77 g/l alcohol (Gorgus et al. 2016). These values are particularly frightening with regard to the food consumption of children. Nevertheless, there is no risk assessment (!) for alcohol in Germany and Europe and also no fixed limit values (!) for the content in food, but one relies on established alcohol consumption guidelines (Seitz and Bühringer 2010).

Caffeine

Similar to alcohol, there are no generally defined limits for the caffeine content in food, but only a health assessment that determines the daily upper limit (BfR; EFSA 2015b). Only three specific food items are subject to limit values: energy drinks (max. caffeine content 320 mg/l (BgVV 2002)) and two approved novel foods (1 mg/kg and 198 - 577 mg/l (EU Kommission 2017)). The BfR and EFSA are of the opinion that the consumption of a single dose of caffeine below 200 mg does not pose any health risks (BfR; EFSA 2015b). EFSA even increases this value to 400 mg caffeine throughout the day, except for pregnant women and nursing mothers, which corresponds to a NOAEL of 5.7 mg caffeine/kg bw (EFSA 2015b). However, this assessment is not based on further derivation of a TDI from this NOAEL using uncertainty factors, but on safety concerns avoided when staying below this certain single and daily dose. If, however, the necessary uncertainty factor of 10 were applied, since a strong interindividual variability in the effects of caffeine is known, a TDI of 40 mg/day (0.57 mg caffeine/kg bw) would already be exceeded by a cup of coffee (83 mg caffeine/150 ml).
Opium alkaloids

The situation is different with so-called opium alkaloids, which include morphine as well as codeine, with the latter known to be converted into morphine in the human liver (Yue and Säwe 1997). In 2011, EFSA established limits for opium alkaloids in poppy seeds, which were confirmed in 2018 after re-examination, with the addition that the concentration of codeine that can be converted to morphine should be taken into account by an uncertainty factor of 0.2. (EFSA 2018). This factor for codeine should correspond to the maximum conversion in human metabolism: up to 20% of codeine can be metabolized to morphine. Thus, the previously established acute reference dose (ARfD) was changed from 0.01 mg morphine/kg bw to 0.01 mg morphine equivalents/kg bw, whereby the possible increase in morphine content in the human body by codeine conversion is not reflected in an adaptation of ARfD. The ARfD of 0.01 mg morphine equivalent/kg bw was determined from the lowest known oral therapeutic single dose of morphine, which was considered the LOEL (lowest observed effect level), and an uncertainty factor of 3. This factor reflects the extrapolation from LOEL to NOEL, but does not contain any interindividual differences, although the same report describes large interindividual differences in morphine effects (EFSA 2018).

However, since the LOEL determined was derived from the pain-relieving effect of morphine in patients, which means there are generally always individual differences in effect, it is incomprehensible that in this case no further uncertainty factor of 10 (as for THC) was assumed. In its opinion of May 2018 EFSA refers to the opinion and the published limit values of the BfR of 2005. In June 2018, the BfR again confirmed the EFSA limit value of May 2018 and stated that the EFSA had established and reconfirmed the ARfD of 0.01 mg morphine equivalent/kg bw by extrapolation from LOEL to NOEL and consider individual differences in sensitivity. However, as explained above, this is not the case because otherwise the uncertainty factor would have to be higher, and suggests that BfR and EFSA, in their coordination and mutual confirmation of their risk assessments, have neglected the thorough reflection and analysis of the same among themselves (BfR 2018a, p. 2). Assuming this ARfD of 0.01 mg morphine equivalents/kg bw for morphine, the consumption of a piece of poppy seed cake or poppy seed roll can exceed this value by a factor of 2, in the worst case even by a factor of 200 when eating a poppy seed roll (Sproll et al. 2016).

Nicotine

The BfR (BfR 2009) as well as the EFSA (EFSA 2009) have assigned nicotine an uncertainty factor of 4.4, which is derived from an uncertainty factor of 10 for interindividual differences and a correction factor of 0.44 for the derivation of oral exposure from study results with intravenously administered nicotine (Table 3).

According to EFSA's opinion on the above-mentioned EIHA position paper (Bañas et al. 2017), for nicotine "very reliable information on the dose-response relationship is available, which made it possible to deduce the extent and severity of the adverse effects observed in LOAEL and to exclude overall the use of a UF for LOAEL-to-NOAEL extrapolation". This means that although there is no experimentally determined NOAEL for nicotine, no uncertainty factor for the extrapolation from LOAEL to NOAEL is estimated in this case. The question that now arises scientifically is how extensive this "very reliable information on the dose-response relationship" has to be in order to allow a renunciation of the extrapolation from LOAEL to NOAEL.

If one compares the BfR risk assessments of nicotine and THC, it is noticeable that only two studies (Lindgren et al. 1999; Woolf et al. 1997) were used for the assessment of the toxic substance nicotine, whereby only the LOAEL of one of the two was used (Lindgren et al. 1999).

In addition, the subjects were smokers and therefore exposed to a daily dose of nicotine. People with a certain "habituation effect", such as to nicotine in this case, naturally react differently to the
intravenous administration of nicotine than non-smokers. This circumstance - following the assessment of the BfR for THC - should, however, have either been included in the risk assessment of nicotine in the form of an uncertainty factor or existing studies with animal experiments should have been used. However, the BfR considers "the extensive data from human studies to be the most suitable basis for the derivation of ARfD for nicotine" (BfR 2009). The EFSA, which comes to the same conclusion in its risk assessment (EFSA 2009), also states that "the LOAEL is considered to be close to the no observed adverse effect level (NOAEL)...", which, together with the "very reliable information on the dose-response relationship..." of nicotine, is sufficient to justify not extrapolating from LOAEL to NOAEL.

In contrast, four studies were used for the risk assessment of THC and two others were cited (see Table 2). In all studies, mainly sick subjects and only partially healthy subjects were given oral phenolic ∆9-THC (dronabinol), while regular cannabis users were excluded. In addition, more recent studies allow the derivation of a NOAEL for the majority of treated individuals and a LOAEL for a few sensitive individuals based on the same dose administered ∆9-THC (Grotenhermen and Müller-Vahl 2012; Hagenbach et al. 2007; Vermersch and Trojano 2016; Wade et al. 2004). Although the data quantity and quality for the risk assessment of THC is significantly better than that of nicotine, the BfR uses a different standard for THC and considers the extensive data situation to be insufficient to dispense with extrapolation from LOAEL to NOAEL. However, the BfR does not point out any reason for this.
Table 2: Various studies used for risk assessment. Listed are the type of literature, the type of subjects, whether they have used cannabis before, the type of THC used, the concentration of THC administered, the parameter considered for the LOAEL (lowest observed adverse effect level) and the NOAEL (no observed adverse effect level) as well as the observed values. It is also noted by which institution the respective study was used for risk assessment and by which institution it was only quoted.

<table>
<thead>
<tr>
<th>Study</th>
<th>Literature type</th>
<th>Test persons</th>
<th>Used form of THC in study</th>
<th>THC concentration</th>
<th>Parameters for LO(A)EL</th>
<th>Parameters for NO(A)EL</th>
<th>NOAEL</th>
<th>Used for risk assessment by</th>
<th>Cited but not used for risk assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Petro and Ellenberger 1981)</td>
<td>primary literature</td>
<td>ill</td>
<td>phenolic Δ⁹-THC (dronabinol)</td>
<td>oral 5; 10 mg/day</td>
<td>5 mg/day</td>
<td>–</td>
<td>–</td>
<td>EIHA</td>
<td>–</td>
</tr>
<tr>
<td>(Chesher et al. 1990)</td>
<td>primary literature</td>
<td>healthy</td>
<td>phenolic Δ⁹-THC (dronabinol)</td>
<td>oral 5; 10; 15; 20 mg/70 kg bw</td>
<td>–</td>
<td>subjective intoxication</td>
<td>5 mg/day</td>
<td>FSANZ; EIHA</td>
<td>BfR; EFSA</td>
</tr>
<tr>
<td>(Struwe et al. 1993)</td>
<td>primary literature</td>
<td>ill</td>
<td>phenolic Δ⁹-THC (dronabinol)</td>
<td>oral 2.5; 5; 10 mg/day</td>
<td>2.5 mg/day</td>
<td>–</td>
<td>–</td>
<td>BfR; EFSA</td>
<td>–</td>
</tr>
<tr>
<td>(Beal et al. 1995)</td>
<td>primary literature</td>
<td>ill</td>
<td>phenolic Δ⁹-THC (dronabinol)</td>
<td>oral 2.5; 5 mg/day</td>
<td>2.5 mg/day</td>
<td>–</td>
<td>–</td>
<td>BfR; EFSA; EIHA</td>
<td>–</td>
</tr>
<tr>
<td>(Beal et al. 1997)</td>
<td>primary literature</td>
<td>ill</td>
<td>phenolic Δ⁹-THC (dronabinol)</td>
<td>oral 2.5; 5 mg/day</td>
<td>2.5 mg/day</td>
<td>–</td>
<td>–</td>
<td>BfR; EFSA; EIHA</td>
<td>–</td>
</tr>
<tr>
<td>(Geiwitz and Ad Hoc Committee on Hemp Risks 2001)</td>
<td>risk assessment; literature review</td>
<td>healthy</td>
<td>total Δ⁵-THC (hemp oil)</td>
<td>oral –</td>
<td>14-21 mg/day</td>
<td>psychoactive effects</td>
<td>5 mg/day</td>
<td>HAH</td>
<td>–</td>
</tr>
<tr>
<td>(Grotenhermen et al. 2001)</td>
<td>risk assessment; literature review</td>
<td>healthy</td>
<td>total Δ⁵-THC (hemp oil)</td>
<td>oral –</td>
<td>2x2.5 mg/day</td>
<td>psychoactive effects</td>
<td>2x2.5 mg/day</td>
<td>HAH</td>
<td>EFSA; BfR</td>
</tr>
<tr>
<td>Study</td>
<td>Subject Type</td>
<td>Treatment</td>
<td>Route</td>
<td>Dose</td>
<td>Effect</td>
<td>Limit</td>
<td>Guideline</td>
<td>Agency</td>
<td>Notes</td>
</tr>
<tr>
<td>------------------------</td>
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<td>-------</td>
</tr>
<tr>
<td>Zajicek et al. 2003</td>
<td>ill</td>
<td>phenolic Δ9-THC (dronabinol)</td>
<td>oral</td>
<td>5 mg/day</td>
<td>subjective sensation: improvement of mobility</td>
<td>5 mg/day</td>
<td>–</td>
<td>–</td>
<td>EIHA</td>
</tr>
<tr>
<td>Ramaekers et al. 2004</td>
<td>–</td>
<td>cannabis</td>
<td>inhalation</td>
<td>–</td>
<td>effects on the central nervous system</td>
<td>2.8 mg/day</td>
<td>–</td>
<td>–</td>
<td>EFSA</td>
</tr>
<tr>
<td>Zajicek et al. 2005</td>
<td>ill</td>
<td>phenolic Δ9-THC (dronabinol)</td>
<td>oral</td>
<td>5 mg/day</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>EIHA</td>
<td>–</td>
</tr>
<tr>
<td>Goodwin et al. 2006</td>
<td>healthy</td>
<td>total Δ9-THC (hemp oil)</td>
<td>oral</td>
<td>0.4; 0.5; 7.5 mg/day</td>
<td>–</td>
<td>–</td>
<td>pharmacodynamic effects</td>
<td>14 mg/day</td>
<td>–</td>
</tr>
<tr>
<td>Ramaekers et al. 2006</td>
<td>–</td>
<td>cannabis</td>
<td>inhalation</td>
<td>0.25; 0.5 mg/kg</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Strasser et al. 2006</td>
<td>ill</td>
<td>total Δ9-THC and other cannabinoids (cannabis extract)</td>
<td>oral</td>
<td>5 mg/day</td>
<td>–</td>
<td>–</td>
<td>any kind of change (e.g. increase in appetite)</td>
<td>5 mg/day</td>
<td>–</td>
</tr>
<tr>
<td>Ballard and de Wit 2011</td>
<td>healthy</td>
<td>phenolic Δ9-THC (dronabinol)</td>
<td>oral</td>
<td>2.5 mg/day</td>
<td>effects on the central nervous system</td>
<td>2.5 mg/day</td>
<td>–</td>
<td>–</td>
<td>BfR</td>
</tr>
</tbody>
</table>
Evaluation of limit and guideline values of THC (tetrahydrocannabinol) in hemp foods

Table 3: Comparison of uncertainty factors of alcohol, opium alkaloids and THC as defined by BfR and EFSA. Listed are the adverse effects, the presence of a NOAEL (no observed adverse effect level), the uncertainty factor defined and its explanation as well as the corresponding reference. * From the point of view of the BfR and the EFSA, effects on the central nervous system, #then still the Federal Institute for Consumer Health Protection and Veterinary Medicine (Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin, BgVV).

<table>
<thead>
<tr>
<th>Substance</th>
<th>Adverse effects*</th>
<th>NOAEL available*</th>
<th>Uncertainty factor</th>
<th>Explanation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>effects on the central nervous system: euphoria, clouding of consciousness, impairment of cognitive abilities and judgement, reduced driving ability and ability to operate machines, aggressiveness, nausea, vomiting, habituation, addiction, addiction, withdrawal symptoms (irritability, dysphoria)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>no risk assessment by the BfR and the EFSA, in Germany there are no limits for alcohol, but alcohol consumption guidelines (Seitz and Bühringer 2010)</td>
</tr>
<tr>
<td>Caffeine</td>
<td>effects on the central nervous system: restlessness, irritability, nervousness, tremors, insomnia, anxiety, habituation, dependence, addiction, withdrawal symptoms (irritability, dysphoria) effects on the vegetative nervous system: increase of heart rate, arrhythmias, vasoconstrictor in the brain, vasodilator in the periphery</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>risk assessment / health assessment by the BfR and the EFSA available, in Germany there are no general limits for the caffeine content in food, but only recommended maximum consumption limits. There are only three specific food limits (see text) (BfR) (EFSA 2015b)</td>
</tr>
<tr>
<td>Nicotine</td>
<td>effects on the central nervous system: dizziness, habituation, dependence, addiction, withdrawal symptoms (irritability, dysphoria)</td>
<td>no</td>
<td>4.4</td>
<td>UF 10 for interindividual differences and a correction factor of 0.44 because oral exposure was derived from study results with intravenously administered nicotine</td>
<td>(BfR 2009) (EFSA 2009)</td>
</tr>
</tbody>
</table>
### Evaluation of limit and guideline values of THC (tetrahydrocannabinol) in in hemp foods

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effects on the central nervous system</th>
<th>Effects on the vegetative nervous system</th>
<th>Evaluation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opium alkaloids (Morphine und codein)</td>
<td>nausea, vomiting, loss of appetite, constipation, sedation, drowsiness, mood changes, euphoria, miosis; Respiratory depression and constipation, changes in the hormonal and autonomic nervous systems.</td>
<td>stimulating, increase in salivary flow, increase in heart rate and blood pressure, narrowing of peripheral blood vessels</td>
<td>UF 3 extrapolation from LOAEL to NOAEL UF 0.2 consideration of conversion of codeine to morphine</td>
<td>(BfR 2005, 2018b) (EFSA 2011b, 2018)</td>
</tr>
<tr>
<td>∆^9-THC</td>
<td>mood swings, fatigue, dizziness, loss of consciousness, insomnia, nausea, euphoria, anxiety, habituation, dependence, addiction, withdrawal symptoms; effects on the vegetative nervous system: increased heart rate, changes in blood pressure</td>
<td>no 20-40 30 various scientific uncertainties UF 3 extrapolation from LOAEL to NOAEL, UF 10 for interindividual differences</td>
<td>(BgVV 1997, 2000) (BfR 2018a) (EFSA 2015a)</td>
<td></td>
</tr>
</tbody>
</table>
1.2 Extrapolation from LOAEL (lowest observed adverse effect level) to NOAEL (no observed adverse effect level)

Regardless of the underlying study and type of THC used, BfR and EFSA apply the highest uncertainty factors, 20-40 and 30, and thus come up with the lowest tolerable daily intake (TDI) values. While the EFSA applies an uncertainty factor of 10 for interindividual differences and a factor of 3 for the extrapolation from LOAEL (lowest observed adverse effect level) to NOAEL (no observed adverse effect level), the BfR gives a range of 20-40, taking into account various scientific uncertainties that are not elaborated. Since, however, the BfR bases its risk assessment on the EFSA assessment ((BfR 2018a), S. 9, 3.1.4.2), a compliant uncertainty factor of 30 is to be assumed.

With few exceptions (Ballard and de Wit 2011; Chesser et al. 1990; Geiwitz and Ad Hoc Committee on Hemp Risks 2001; Goodwin et al. 2006; Grotenhermen et al. 2001), the studies used for risk assessment by BfR and EFSA and other various institutions (Table 2) are medical studies for the treatment of various clinical pictures (e.g. epilepsy, anorexia) with THC. The lowest dose of phenolic ∆9-THC (hereinafter referred to as ∆9-THC) administered in these studies was 2.5 mg/day and was in most cases derived as LOAEL for the endpoint of central nervous side effects (Table 2).

However, these clinical studies show that in most cases a significantly higher dose than 2.5 mg/day was and is necessary for either the desired therapeutic effect or an adverse effect to be noticed by the patient (e.g. (Grotenhermen and Müller-Vahl 2012; Hagenbach et al. 2007; Vermersch and Trojano 2016; Wade et al. 2004)).

It is well known that interindividual sensitivity to THC effects in the population can vary considerably. For this reason, the treatment principle "start low, go slow" applies in medical practice in order to rule out pronounced side effects even in sensitive persons. According to this principle, in general, a starting dose of 2.5 mg THC is administered once or twice a day and increased by a further 2.5 mg daily or every 2-3 days until the desired or undesired effects occur (Grotenhermen and Häußermann 2017). For the treatment of spinal cord injury-related spasticity with orally administered ∆9-THC, for example, various study participants required between 15-60 mg/day in order to achieve a therapeutic effect (Hagenbach et al. 2007). In a clinical study involving 160 multiple sclerosis patients, individual sensitivity to desired and adverse effects varied between 2.5 and 120 mg daily ∆9-THC (Wade et al. 2004).

Thus the 2.5 mg/day LOAEL are the effective threshold for sensitive persons and therefore represent instructions for starting a treatment so that sensitive persons do not experience any strong side effects. Only from this amount or higher an effect is possible and expectable, especially since below the threshold of 2.5 mg/day no central nervous effects have been known or determined.

When Sativex® cannabis extract is used to treat multiple sclerosis-related spasticity, the average effective doses are 6-7 sprays per day, which corresponds to a ∆9-THC dose of approximately 16-19 mg/day (Vermersch and Trojano 2016). This is therefore an average dose that is so well tolerated with regard to central nervous side effects that it does not have a relevant effect on everyday life, but at the same time is therapeutically effective.

In conclusion, this means that a dose of 2.5 mg/day is de facto a NOAEL for the majority of healthy and ill persons, whereas for a few sensitive persons it is a LOAEL.

Due to this differentiated perspective on the effective dose of ∆9-THC, which is supported by a large number of current studies (see overviews of (Grotenhermen and Müller-Vahl 2012, 2016; Hagenbach et al. 2007; Vermersch and Trojano 2016; Wade et al. 2004)), a well-founded scientific basis is provided for avoiding extrapolation from LOAEL to NOAEL, as is the case with nicotine (see 1.1). In light of these studies, the current risk assessment of THC by the BfR is insufficient and should therefore be revised.
1.3 Risk assessment based on studies with phenolic $\Delta^9$-THC for the treatment of critically ill test persons

In 5 out of 8 cases, studies with phenolic $\Delta^9$-THC based on the treatment of "seriously ill test persons" were used for risk assessment (Table 2). However, the BfR does not take into account that food (which includes hemp food) is primarily intended for "healthy" people to eat and maintain their health, but not for the treatment or care of "sick people". Significantly, the EFSA and the EU Commission have used only studies carried out on healthy volunteers for the assessment of "health claims" for food, whereas clinical studies on sick volunteers generally have the disadvantage that possibly relevant physiological parameters of the volunteers have been altered and the volunteers generally receive other treatments or medications (BfR 2008). This scientific principle must, of course, be observed not only in health-related effects but also in risk assessment.

1.4 Distinction between total $\Delta^9$-THC und $\Delta^9$-THC

The differentiation between total $\Delta^9$-THC and phenolic $\Delta^9$-THC is of great importance for the risk assessment of THC contents in hemp food, because in fresh hemp and petals phenolic $\Delta^9$-THC is only present up to approx. 10%, up to 90% constitutes the non-psychoactive $\Delta^9$-THC precursor $\Delta^9$-THCA-A (tetrahydrocannabinolic acid A; tetrahydrocannabinolic acid A) (Jung et al. 2009). The conversion (decarboxylation) of $\Delta^9$-THCA-A to phenolic $\Delta^9$-THC, hereinafter referred to as $\Delta^9$-THC, and thus the increase of the $\Delta^9$-THC content in hemp food depends on the respective production and processing methods. If the hemp food is heated over a longer period of time (from 85 °C), a conversion from $\Delta^9$-THCA-A to $\Delta^9$-THC is to be expected, which increases with rising temperature (Bañas et al. 2017). However, a complete conversion from $\Delta^9$-THCA-A to $\Delta^9$-THC under normal food and food production and preparation conditions is almost impossible.

Most institutions consider studies using phenolic $\Delta^9$-THC (dronabinol) for risk assessment of THC. Only one institution, the Croatian Food Agency (HAH) (HAH 2011), cites and draws on risk assessment studies that address the mode of action of total $\Delta^9$-THC (Geiwitz and Ad Hoc Committee on Hemp Risks 2001; Grotenhermen et al. 2001). Three other institutions - including the European Food Safety Authority (EFSA) - base their risk assessment on studies with phenolic $\Delta^9$-THC.

This alone makes it clear that for the risk assessments of the EFSA and other institutions such as the BfR, which use the studies with $\Delta^9$-THC as a basis, inaccurate and unrealistic basic assumptions are made for the intake of THC. Because, as mentioned above, in hemp-containing food there is total $\Delta^9$-THC ($\Delta^9$-THCA-A and $\Delta^9$-THC) and not only $\Delta^9$-THC. Thus, a tolerable daily intake (TDI) is determined on the basis of the mode of action of $\Delta^9$-THC from which in turn guideline values for the total $\Delta^9$-THC content in food are derived, although this is already disproportionate and therefore incorrect as known from the facts described above. This is because the sole share of the $\Delta^9$-THC in the measured total $\Delta^9$-THC content in hemp food is actually significantly lower. This topic about the currently used and undifferentiated analytical methodology (no differentiation of total $\Delta^9$-THC and $\Delta^9$-THC content) for the purpose of risk assessment is explained in more detail in Chapter 2.

1.5 Conclusion

As mentioned at the beginning, there are no predefined standards for the risk assessment of different substances. Although EFSA’s guidelines (EFSA 2012) provide recommendations, their application is always at the discretion of the respective assessment expert; the same apparently seems to apply to the BfR. However, as could be shown in the present analysis, these recommendations are not
sufficient to guarantee a scientifically sound and differentiated risk assessment of substances, which leads to rather inconsistent, intransparent and hardly comprehensible assessments.

Therefore, the following aspects should be considered in a new, up-to-date risk assessment:

- Addition of studies on healthy volunteers and consideration of suitable and current scientific literature which, when considered in a differentiated way, permit and justify the derivation of a NOAEL for Δ⁹-THC.
- Early coordination of BfR and EFSA on a new recommendation for the maximum daily intake of phenolic Δ⁹-THC and derivation of new guideline values for maximum contents of phenolic Δ⁹-THC in food.
- Orientation of the official analytical methods of the national states towards the measurement of phenolic Δ⁹-THC in food.

2 Derivation of guideline values and determination of the Δ⁹-THC content in food

The guideline values for the total Δ⁹-THC content in food have been derived from the tolerable daily intake (TDI) for Δ⁹-THC and determined by the BfR 1997 (then still BgVV) (BgVV 1997).

2.1 Establishment of guideline values for THC content in food

In their comments on the derivation of the guideline values (BfR 2018a; BgVV 1997, 2000), the BfR made a scientific error.

In its first statement on the use of hemp in food (BgVV 1997), the BfR (then still BgVV) together with the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) set maximum daily exposure limit values of 0.001 - 0.002 THC mg/kg body weight (BgVV 1997; DFG 2005). Here they refer to a human study "...with 31 AIDS patients who received this dose (2.5 mg/person/day) orally daily for two weeks." (DFG 2005). Unfortunately, the BfR and the DFG failed to provide a literature reference for this study.

However, based on other studies published at that time (Beal et al. 1995; Struwe et al. 1993), it can be assumed that the administered dose of 2.5 mg/person/day is phenolic Δ⁹-THC (hereinafter Δ⁹-THC), so-called dronabinol. But this important distinction between the total Δ⁹-THC and the Δ⁹-THC and its necessity for a scientifically sound definition of a TDI cannot be found in the BfR and the DFG statement. They speak only of THC: "Despite the shortcomings of this study, one could deduce from its findings that repeated intake of 2.5 mg THC/day from food in adults appears to be likely to produce effects that should be regarded as adverse health effects. Such intake is expected, for example, when hemp oil containing 250 mg THC/kg is consumed in quantities of 10 g/day." (DFG 2005). This lack of differentiation is not made up for or self-reflected at any later point in time (BfR 2018a; BgVV 1997, 2000). These TDI's are declared and confirmed as Δ⁹-THC (BgVV 1997, 2000).

The recommendation, published in 1997 by the BgVV, not to exceed a maximum intake of 0.001-0.002 mg Δ¹-THC/kg bw is also based on a LOAEL (lowest observed adverse effect level) for central nervous effects of 2.5 mg Δ⁹-THC/kg bw (corresponding to 0.040 mg/kg bw assuming 60 kg bw) and a safety factor of 20-40 to take account of open scientific questions, identified within the framework of an unnamed human study (BgVV 1997). From this, however, guideline values for the total Δ⁹-THC content (Δ¹-THC and its precursor Δ⁹-THCA-A) in food are derived, which is – as described above – not correct, since the proportion of Δ⁹-THC in food in the measured total Δ⁹-THC content is significantly lower than when determined in this way.
In principle, the BfR distinguishes between various hemp-containing food groups, namely between non-alcoholic and alcoholic beverages, edible oils and all other foods, and sets guideline values for these food groups total $\Delta^9$-THC content. These are 0.005 mg/kg for non-alcoholic and alcoholic beverages, 5 mg/kg for edible oils and 0.15 mg/kg for all other foods.

### 2.2 Measurement methodology for the determination of the total $\Delta^9$-THC content

The described and incorrect use of the total $\Delta^9$-THC content was probably due to the measurement methodology accepted and available at that time: In the official German collection for the analysis of food according to § 64 LFGB (German Food and Feed Code) there are only two analytical methods for hemp products, both of which can only determine the total THC content. The analytical method BVL L13.04.19-1 (BVL 2000) is used to determine the total $\Delta^9$-THC content in hemp oil and BVL L47.00-9 (BVL 2004) is used to determine the total $\Delta^9$-THC content in hemp-containing tea-like products (direct determination in dry material).

However, as explained in chapter 1, hemp food does not only contain $\Delta^9$-THC, but total $\Delta^9$-THC, i.e. the non-psychoactive $\Delta^9$-THC precursor $\Delta^9$-THCA-A and the psychoactive $\Delta^9$-THC. However, it is not possible to distinguish between the $\Delta^9$-THC precursor and $\Delta^9$-THC with the currently officially accepted and used analytical methods for the determination of the $\Delta^9$-THC content in food; both are measured "as a sum" and this is then indicated as the $\Delta^9$-THC content in food. Considering the fact that the non-psychoactive precursor $\Delta^9$-THCA-A is present in the plant in significantly higher quantities than $\Delta^9$-THC (in fresh leaves and flowers 90% $\Delta^9$-THCA-A and 10% $\Delta^9$-THC; (Jung et al. 2009)) and thus, depending on the processing, also in the food, the current method therefore measures significantly higher $\Delta^9$-THC values for food than are actually contained.

The determination of $\Delta^9$-THCA-A by the above-mentioned methods is impossible because the samples are heated to 250 °C during evaporation in the injector for the purpose of sample introduction onto the GC column. This leads to a falsification of the original $\Delta^9$-THC content during the analysis, because from 85 °C $\Delta^9$-THCA-A decarboxylates to $\Delta^9$-THC (Baňas et al. 2017) and thus increases the $\Delta^9$-THC content in the measured food sample. To what extent and whether the $\Delta^9$-THCA-A is completely transformed into $\Delta^9$-THC by the above-mentioned official methods can unfortunately not be seen from the method description for the determination of total $\Delta^9$-THC in e.g. hemp oil, because the method is only calibrated with pure $\Delta^9$-THC. $\Delta^9$-THCA-A is neither tested at all for calibration nor is its recovery rate determined under the given measurement parameters.

This means, therefore, that the total $\Delta^9$-THC contents in food determined by the BfR (see Figure 5 (BfR 2018a)) do not reflect the actual amount of $\Delta^9$-THC contained. The BfR is aware of this inadequacy of the recognised method used and "... notes that the exact contents of $\Delta^9$-THC in different food cannot currently be determined exactly due to the known methodological limits and the uncertainties resulting for the analytical determination of the $\Delta^9$-THC contents in different food" and also clearly points out that this has to be improved so that a distinction can be made between precursor and $\Delta^9$-THC so that the $\Delta^9$-THC content can be determined explicitly.

Nevertheless, the BfR concludes that "... the proposed approach leads to results which take sufficient account of the existing uncertainties". Thus, the BfR bases its current statement "Tetrahydrocannabinol contents are too high in many hemp-containing foods - health impairments are possible" (BfR 2018a) on the results of an inadequate research methodology and compares values that are not comparable with each other, namely total $\Delta^9$-THC content with the tolerable daily intake of phenolic $\Delta^9$-THC (Figures 3, 4, 6 and 7 (BfR 2018a)), and thus concludes that the $\Delta^8$-THC contents in foods are much too high.

In particular, it is inadmissible to calculate the theoretical total consumption of $\Delta^9$-THC until the EFSA-derived ARfD of 0.001 mg $\Delta^9$-THC /kg bw is reached (as shown in Figure 3 (BfR 2018a)) and to compare it with BgVV guideline values (see 2.1) for total $\Delta^9$-THC, because the ARfD from EFSA is derived from studies with phenolic $\Delta^9$-THC. Instead, at least the theoretical amount consumed until
the maximum daily intake of 0.002 mg total $\Delta^9$-THC/kg bw derived from the BgVV and DFG (see 2.1) should have been used for calculation. This means we find here a falsification by a factor of 2, which leads to objectively inaccurate results and scientifically completely wrong conclusions for the risk assessment of $\Delta^9$-THC.

### 2.3 Thermal conversion from $\Delta^9$-THCA-A to $\Delta^9$-THC

With regard to the possible thermally induced conversion of the precursor $\Delta^9$-THCA-A to $\Delta^9$-THC in food, the following should be noted:

The guideline values determined by the BgVV (provisional guide values) refer to the ready-to-eat food and apply to the total $\Delta^9$-THC (BgVV 2000). Most hemp products are offered ready-to-eat. Depending on the production and preparation, the shares of $\Delta^9$-THCA-A and $\Delta^9$-THC in the total $\Delta^9$-THC are very different. In the case of heated products (e.g. baked goods), the $\Delta^9$-THC content may predominate, but $\Delta^9$-THCA-A is generally still present in a considerable proportion (approx. 57%), as an example of baking with hemp flour shows: A cake has an internal temperature in the oven of less than 100 °C (as long as water is present). With an average baking time of 45 minutes, this would mean that only about 1/3 of the $\Delta^9$-THCA-A is converted to $\Delta^9$-THC. Therefore, the realistic proportion of $\Delta^9$-THC in hemp flour after baking is 43% of the total $\Delta^9$-THC (33% by converting $\Delta^9$-THCA-A to $\Delta^9$-THC and 10% of the original $\Delta^9$-THC content in hemp flour) (Bañas et al. 2017).

In order to adequately assess the marketability of hemp products, therefore, official analytical methods are required which can quantitatively determine both $\Delta^9$-THC and $\Delta^9$-THCA-A. Only those products remain problematic for risk assessment that

1. are not offered ready-to-eat,
2. and / or are heated again after purchase by the consumer (whereby the $\Delta^9$-THC content could increase)

Case 1. can be addressed by the manufacturer giving a standard formulation for the preparation as a recommended daily intake and maximum daily intake for adults (possibly together with restrictions for certain population groups, i.e. children or pregnant women). Such products would be e.g. hemp teas or hemp protein preparations. For the risk assessment of hemp teas we refer to the procedure which is used in Switzerland and which is described in the „Ordinance of the Federal Department of Home Affairs on the maximum contents for contaminants“ for the substance "Tetrahydrocannabinol, Delta9-" (EDI 2016). Here, a standard recipe for the preparation of herbal and fruit teas with all the necessary parameters to make it reproducible for analysis is given.

Case 2. can be solved by the manufacturer advising the consumer not to heat the product. With hemp seed products and in particular hemp oil, heating makes no sense anyway, because the valuable polyunsaturated fatty acids would decompose easily.

### 2.4 Conclusion

The evaluations and findings of the BfR in its assessment of the THC content in hemp foods are incorrect and require urgent revision.

For a revised, more up-to-date and scientifically correct determination of THC contents in hemp foods, the following aspects have to be considered:

- Validation and introduction of official analytical methods that can quantitatively determine both $\Delta^9$-THC and $\Delta^9$-THCA-A.
- Evaluation of the marketability of hemp products exclusively according to the determined content of $\Delta^9$-THC.
• Measurement of total Δ⁹-THC in food as a transitional solution if the guideline values for total Δ⁹-THC in food are appropriately increased.
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