BfR

Bundesinstitut für Risikobewertung

Tetrahydrocannabinol levels are too high in many hemp-containing foods - health impairments are possible

BfR Opinion No 034/2018 of 8 November 2018

Various hemp-containing foods are available on the market. These include tea-like herbal mixtures consisting entirely or partially of hemp leaves. The German Federal Institute for Risk Assessment (BfR) has assessed the risk of psychogenic and pharmacological effects for all population groups, including children, through the consumption of hemp-containing foods containing customary levels of tetrahydrocannabinol as determined by the monitoring authorities. On the basis of the available data, BfR comes to the following conclusion: consumption of hemp-containing foods with the total Δ^9-tetrahydrocannabinol (Δ^9-THC) levels on which the calculation is based can lead to an exceedance of the acute reference dose (ARfD) of 0.001 milligrams (mg) per kilogram body weight proposed by EFSA. This acute reference dose describes the quantity of Δ^9-THC which can be ingested in the short term without the expectation of any psychomotor and psychogenic effects. Consuming hemp-containing foods, it is also possible that Δ^9-THC doses could be ingested which lie within the range of the doses of ≥ 2.5 milligrams (mg) per person and day used in pharmaceutical products. In this case, pharmacological effects would be expected. As the occurrence of psychomotor effects such as reduced reaction capability or tiredness has to be expected in this dose range, restrictions in a person's ability to drive or operate a dangerous piece of machinery may result from the consumption of foods containing hemp. This applies in particular to high consumers of products of this kind. The psychomotor effects can also be enhanced by the consumption of alcohol and certain other drugs. In the opinion of the BfR, levels of Δ^9-THC in hemp-containing foods should therefore be further minimised.

BfR Risk Profile: Tetrahydrocannabinol levels are too high in many hemp-containing foods – health impairments are possible (Opinion No. 034/2018)				
A Affected groups	**1 Children** **2 General population**			
B Probability of a health impairment through [describe exposure]	Practically excluded	Unlikely	**Possible**	Probable	Certain
C Severity of the health impairment through [describe exposure]	No impairment	**Slight impairment [reversible]**	Moderate impairment [reversible/irreversible]	Severe impairment [reversible/irreversible]
D Reliability of available data	High: The most important data are available and are free of contradiction	**Moderate: Some important data are missing or contradictory**	Low: Numerous important data are missing
E Controllability by the consumer	Control not necessary	Controllable through precautionary measures	**Controllable through avoidance**	Not controllable

Squares highlighted in dark blue indicate the properties of the risk assessed in this Opinion (more detailed information on this is contained in BfR Opinion No. 034/2018 of 8 November 2018).

Explanations

The risk profile is intended to visualise the risk outlined in the BfR Opinion. It is not intended for the purpose of comparing risks. The risk profile should only be read in conjunction with the corresponding opinion.

1.   Subject of the assessment

Upon request of a monitoring authority of one of Germany's federal states (Bundesl*änder*), the Federal Ministry of Food and Agriculture (BMEL) commissioned the German Federal Institute for Risk Assessment (BfR) to evaluate the following fundamental aspects with regard to the assessment of tetrahydrocannabiol (Δ9-THC) levels in – in particular – tea-like products containing hemp as well as other hemp-containing foods:

(1)   Design of the analytical process for the determination of the Δ9-THC level in tea-like products containing hemp

The federal state authority proposes that at first the total Δ9-tetrahydrocannabinol (total-Δ9-THC) content in dry material be determined using a method developed by an ASU working group in 2002. Based on the assumption of full carryover, these data for the raw material should be used as a basis for the calculation of the Δ9-THC level in the ready-to-drink infusion of tea-like products containing hemp. In order to judge these levels, the guidance value for maximum Δ9-THC levels for alcoholic and non-alcoholic beverages established by the Federal Institute for Consumer Health Protection and Veterinary Medicine (BgVV) in the year 2000 should be considered.

(2)   A review to determine whether the guidance values established for maximum Δ9-THC levels in foods in 2000 are still suitable from a toxicological point of view as a basis for risk assessment

2   Result

This Opinion discusses the aforementioned aspects against the backdrop of the data that are currently available.

(1)   Design of the analytical process for the determination of the ∆9-THC content in tea-like products containing hemp

In order to assess the ∆9-THC content of tea-like products containing hemp, the state authority proposes that at first the total ∆9-THC content (sum of 2-carboxy-∆9-THC (∆9-THCA-A) and ∆9-THC) be determined in the dry material by means of the official analytical method ASU L 47.00-9:2004-12.Based on the assumption of full carryover, and taking into account the product-dependent ratio of dry material and water, the measured content in the dry material should then be converted to arrive at the content in a ready-to-drink infusion, , and. The guidance value for maximum ∆9-THC levels for non-alcoholic and alcoholic beverages established by the BgVV in the year 2000 should then be used to judge the total ∆9-THC content.

In this context, the BfR notes that, due to the known methodological limitations and the resulting uncertainties with regard to the analytical determination of ∆9-THC levels in different foods, it is currently not possible to precisely determine the exact levels of ∆9-THC in different foods. As outlined in detail in section 3.2.2, the following uncertainties are considered to be of particular relevance:

•   The use of different analytical methods for the determination of the ∆9-THC content; some methods measure the total ∆9-THC level, while other methods selectively measure only ∆9-THC.
•   Uncertainties with regard to the extraction efficiency of ∆9-THCA-A and ∆9-THC in dependence on the sample matrix and extraction method in question
•   Uncertainties with regard to the carryover of ∆9-THCA-A or ∆9-THC from the dry material to the aqueous infusion
•   Uncertainty with regard to the conversion of ∆9-THCA-A into ∆9-THC during food processing

These uncertainties can result in both underestimation and overestimation of the actual ∆9-THC content. In consideration of all relevant aspects, the BfR comes to the conclusion that the proposed procedure supplies results that do sufficiently allow for the aforementioned uncertainties.

(2)   A review to determine whether the guidance values established for maximum ∆9-THC levels in foods in 2000 are still suitable from a toxicological point of view as a basis for risk assessment

As no consumption data are available for hemp-containing foods, it was not possible to conduct an exposure assessment in the classic sense. The potential health risks were therefore assessed using model calculations.

The first step was to review whether, on the basis of the consumption data that are currently available, the guidance values established for maximum Δ9-THC levels in foods in 2000 are still suitable for risk assessment from a toxicological point of view.

Hemp-containing foods belong to the category of seldomly consumed foods. Consequently, no robust consumption data are available for children or adults. Based on the assumption that Δ9-THC contents in hemp-containing foods are still just within the guidance values of the BgVV, the theoretical consumption quantities of hemp-containing foods were calculated for children and adults at which the acute reference dose (ARfD) would be reached (Figures 3 and 4). These consumption quantities are compared with the consumption quantities of analogous foods that do not necessarily contain hemp calculated using the data from the National Nutrition Survey II (NVS II) or Consumption Survey of Food Intake among Infants and Young Children (VELS). This procedure is based on the assumption that hemp-containing and analogous foods are consumed in similar quantities (based on a single day).

Based on this model calculation, it is possible that the ARfD is already clearly exceeded due to consumption of individual food groups (in the categories "edible oils" and "all other foods"; Figures 3 and 4), at least in the case of high consumers. This is particularly true in children. The model calculation shows that exceeding the ARfD is possible despite compliance with the BgVV guidance values.

The second step was to examine exposure based on real data for levels of total Δ9-THC in foods containing hemp.

These data show that the existing guidance values for Δ9-THC levels in hemp-containing foods are markedly exceeded in some cases. This applies to tea-like products containing hemp, hemp oil, hemp seeds and food supplements. Due to a lack of data on the consumption of hemp-containing foods, the assessment of potential health risks was based on a model calculation. The real data on total Δ9-THC levels were used to calculate the theoretical consumption quantities, at whichthe ARfD would be reached.

The model calculation shows that the ARfD for Δ9-THC may be clearly exceeded due to consumption of hemp-containing foods, at least in the case of high consumers. Here again, this comparison scenario indicates that exceedance is particularly pronounced in the case of children.

The BfR is of the opinion that the consumption of hemp-containing foods with the underlying total Δ9-THC levels may result in an exceedance of the ARfD. Moreover, it also appears possible that the consumption of foods containing hemp might result in the intake of Δ9-THC doses in the range of the pharmaceutically administered doses of ≥ 2.5 mg per person and day. In this case,the occurance of pharmacological effects must be expected. As psychomotor effects must also be expected in this dose range, consumption of hemp-containing foods may also result in restrictions in a person's ability to drive or operate a dangerous piece of machinery. The psychomotor effects can also be intensified by the consumption of alcohol and certain other drugs.

(3)   Further relevant aspects

In the seeds of hemp plants,cannabinoids are generally not formed. The low amounts of occurring Δ9-THC in seeds are primarily seen as the result of contamination due to contact with parts of the plant that contain Δ9-THC. The BfR therefore believes that the levels in the seeds of the hemp plants and the food made from them can be reduced by taking suitable process-related measures. This would then prevent exceedance of the guidance values in the corresponding foods or exceedance of the ARfD.

With the exception of seeds and roots, all parts of the hemp plants have glandular hairs that produce a resin containing cannabinoids. This means Δ9-THC is a natural constituent of all tea-like products containing hemp, particularly if these products are made of hemp leaves and hemp flowers. The Δ9-THC content may fluctuate markedly depending on the variety of hemp and various environmental factors. In the view of the BfR, it is questionable whether it is possible to reliably reduce Δ9-THC levels in these foods in order to avoid exceedance of the guidance values in the corresponding hemp-containing foods or exceedance of the ARfD.

Alongside the use of hemp-containing foods for the intended purpose, the BfR also sees the possibility of the misuse of certain products containing hemp. , Hemp leaves and flowers appear as being of particular relevance with respect to a potential misuse.

3   Reasons

3.1   Risk assessment

3.1.1 Possible sources of hazard

A wide selection of hemp-containing foods are commercially available. In addition to hemp seeds and the hempseed oil made from the seeds, retailers also offer various other hemp-containing foods such as baked goods, beer or tea-like products. The latter products consist partly or entirely of hemp leaves and sometimes hemp flowers. The hemp grown for fibre production which is generally used in food production may contain up to 0.2 % Δ^9-THC. As a consequence, for example Lachenmeier et al. reported on Δ^9-THC levels of up to 2.4 mg/kg in infusions of tea-like products containing hemp (Lachenmeier 2004).

3.1.2   Agent

The hemp plant *Cannabis sativa* L. belongs to the Cannabinaceae family and is an annual, dioecious plant. This plant has been cultivated as a crop plant for many centuries and serves in particular to provide the fibres used in sectors such as the textile industry. The protein and fat-rich seeds are used to obtain hemp oil and are also used as feed. Moreover, various preparations of the plant have been used as natural remedies since antiquity, but also as intoxicating drugs. When used for intoxication, preparations made from the plant are generally smoked, with oral intake – e.g. in the form of hemp-containing biscuits– being less frequent (EFSA 2011; Hänsel and Sticher 2007; Hazekamp 2009; Marquardt and Schäfer 2004; WHO 2016).

To date, more than 560 different substances have been identified in the hemp plant (ElSohly *et al.* 2017). The seeds contain a high level of fatty oil (25-35 %) and protein (20-25 %) and supply all the essential amino acids and fatty acids for human nutrition. The fatty acid profile

exhibits a high percentage of unsaturated fatty acids – in particular linoleic and linolenic acid in a ratio of 3:1 – and is therefore considered to be nutritionally valuable (Leizer *et al.* 2000).

With the exception of seeds and roots, all parts of the hemp plant have glandular hairs that produce a resin with a 80-90 % cannabinoid content. Cannabinoids occur exclusively as secondary plant components in the hemp plant. The cannabinoid content correlates with the number of glandular hairs. These hairs are particularly dense on leaves in the area of the infloresences. Female plants generally have more and larger glandular hairs (Lachenmeier 2004). More than 120 different cannabinoids have been identified to date (Wang *et al.* 2017).

Cannabinoids do not occur in the seeds due the absence of glandular hairs (Hänsel and Sticher 2007; Lachenmeier 2004; Marquardt and Schäfer 2004; Ross *et al.* 2000). It is assumed that the cannabinoid Δ^9-THC detected in the seeds is primarily a result of contamination caused by contact with parts of the plant that are rich in Δ^9-THC during harvesting or processing (Ross *et al.* 2000).

Δ^9-THC is considered to be the main agent responsible for the psychoactive effect of cannabis products. The other main types of cannabinoids occurring in the plant are cannabinol (CBN) and cannabidiol (CBD) (Hänsel and Sticher 2007; WHO 2016). A distinction is made between varieties of hemp grown for the production of drugs (Δ^9-THC level above 1 %) and hemp grown for fibre (Δ^9-THC level below 0.25 %) (Teuscher *et al.* 2004). The ratio of (Δ^9-THC+CBN)/CBD also permits classification of the plant in this way (hemp grown for drugs: ratio > 1; hemp grown for fibre: ratio < 1) (Lachenmeier 2004).

Δ^9-THC is formed in the hemp plant from Δ^9-THC carboxylic acids, in particular 2-carboxy-Δ^9-THC (Δ^9-THCA-A) (EFSA 2015). According to a publication by Jung et al. (2009) cited by EFSA (2015), approx. 90 % of the total Δ^9-THC in the fresh plant material (based on the sum of Δ^9-THCA-A and Δ^9-THC takes the form of Δ^9-THCA-A, which does not itself possess any psychoactive effect. However, this statement is not supported by any experimental findings in the publication of Jung et al. The available literature contains widely varying figures on the ratio of Δ^9-THCA-A to Δ^9-THC in the hemp plant (Aizpurua-Olaizola *et al.* 2014; Baker *et al.* 1981; De Backer *et al.* 2009; Rovetto and Aieta ; Wang *et al.* 2017). The ratio of the two compounds is evidently subject to high levels of fluctuation. Δ^9-THC can basically be present in four different isomers, but only (-)-trans-Δ^9-THC is formed naturally (EMCDDA). This substance is hardly soluble in water (2.8 mg/L at 23 °C), but is easily soluble in various organic solvents. There is no experimental data on the solubility of Δ^9-THCA-A. Dronabinol is the international non-proprietary name for synthetic Δ^9-THC (EMCDDA).

Alongside Δ^9-THC, there are many other cannabinoids that are described as having pharmacological effects. In particular, numberousstudies on CBD are available. In addition to direct pharmacological effects, modification of the effects of Δ^9-THC may also be caused by other cannabinoids contained in the hemp plant. The little data that have been published are contradictory and do not permit any definitive assessment of the individual effects or interactions (EFSA 2015; Izzo *et al.* 2009). CBD as a medication is already being investigated in clinical studies (O'Connell *et al.* 2017).

This Opinion confines itself to answering the specific questions relating to Δ^9-THC.
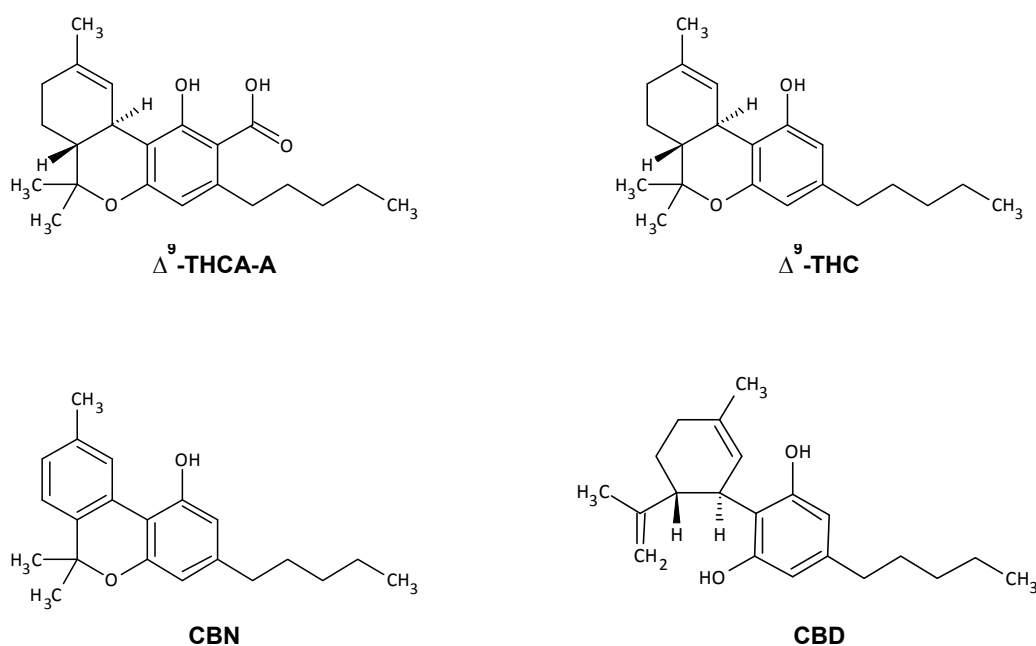
Figure 1: Structures of selected cannabinoids of the hemp plant

3.1.3 Δ^9-THC in foods and as a medication

Currently,no standardised maximum levels for Δ^9-THC in foods are set in the EU. In the year 2000, the BgVV published values for maximum Δ^9-THC levels in various food groups. These levels are 0.005 mg/kg for non-alcoholic and alcoholic beverages, 5 mg/kg for edible oils and 0.150 mg/kg for all other foods, and they refer to ready-to-eat foods (BgVV 2000).

Δ^9-THC and preparations of *Cannabis sativa* L. are also used for medicinal purposes in various countries. In Germany, for example, medicinal hemp varieties specially grown under controlled conditions are used for this purpose. The standard method is to produce an aqueous infusion from the leaves and flowers. Alternatively, extracts obtained from the hemp plant or Dronabinol (in other words, synthetically produced Δ^9-THC) are used for therapeutic purposes (BfArM 2017; FDA 2004; GW Pharma 2015; Hänseler AG 2014). In Germany, all these preparations are subject to the relevant laws governing medicines and narcotics. They are used, for example, to treat cytostatic-induced nausea and vomiting as well as to increase appetite in AIDS patients. Depending on indication, the standard initial doses are in the order of 2.5 mg Δ^9-THC per day, with maximum daily doses of 20 mg. In this dose range, undesired medication effects include a "high" feeling, dizziness, euphoria, paranoia, tiredness, concentration problems, nervousness, confusion, nausea, vomiting, abdominal pain, diarrhoea, palpitations, tachycardia and effects on blood pressure. The occurrence of these undesired effects is dose-dependent and differs considerably between individuals, and these undesired effects often decrease over the course of long-term therapy. There is a possibility of physical and psychological dependence, but this is rare and not very pronounced. The literature describes the development of tolerance towards some effects of

Δ^9-THC (FDA 2004; GW Pharma 2015; Hänseler AG 2014). During medicinal therapy with Δ^9-THC, a person's ability to drive road vehicles or operate dangerous machinery may be compromised due to possible psychomotor effects. When Δ^9-THC is used for medical purposes, therefore, patients must be advised that they can only perform these activities during the later course of the therapy, after/if it has been proven that these impairments do not or no longer exist (FDA 2004; Hänseler AG 2014). It is likely that other cannabinoids will be used for medicinal purposes in the future, and clinical studies are already investigating above all the therapeutic administration of CBD (O'Connell *et al.* 2017).

3.1.4   Hazard potential

3.1.4.1 Assessments of national and international authorities

The hazard potential of Δ9-THC in foods has already been assessed by various national and international institutions.

In 1997, BgVV published an opinion on the use of hemp in foods. In order to assess the possible health risks to humans following oral intake of Δ9-THC, BgVV identified effects on the central nervous system as the most sensitive endpoint. The opinion pointed out that effects of this type can already be observed at a dose of 2.5 mg Δ9-THC/person (equivalent to 0.040 mg/kg body weight (bw) based on a bodyweight of 60 kg). The dose of 0.040 mg/kg bw therefore served as a reference point. Using a safety factor of 20-40 to take account of various scientific uncertainties, BgVV recommended that a daily intake of 0.001-0.002 mg Δ9-THC/kg bw should not be exceeded (BgVV 1997).

In the year 2002, the Food Standards Australia New Zealand (FSANZ) derived a value for the tolerable daily intake (TDI) of Δ9-THC in foods. Based on data from a human study by Chesher et al. (1990), FSANZ identified changes in "skill performance" as the most sensitive endpoint. Oral doses of 0, 5, 10, 15 and 20 mg Δ9-THC were administered to healthy individuals during this study. The dose of 5 mg (equivalent to 0.060 mg/kg bw) was seen as the lowest observed effect level (LOEL) and served as a basis for the derivation of the TDI of 0.006 mg/kg bw (ANZFA 2002) using an uncertainty factor of 10 to allow for inter-individual differences. A subsequent opinion published in 2012 also considered this TDI to be protective (FSANZ 2012).

In 2011, the Croatian Food Agency assessed the health-related consequences of the intake of Δ9-THC through consumption of foods containing hemp (HAH 2011). The opinion was based on an acceptable daily intake (ADI) of 0.500 mg Δ9-THC/person which had been published in a review by Grotenhermen et al. (2001).

The European Food Safety Authority (EFSA) assessed the safety of hemp as feed in 2011 (EFSA 2011).

In 2015, EFSA published an opinion on Δ9-THC in foods. This opinion described and assessed the available and relevant data on the hazard potential of Δ9-THC in detail. The opinion states that following oral intake of low doses of
Δ9-THC, particularly effects on the central nervous system and the cardiovascular system might be expected in humans. As effects were already observed at the lowest investigated doses, it was not possible to derive a NOAEL (no observed adverse effect level). Moreover,

the available human data did not permit any modelling of the dose-effect relationship. Effects on the central nervous system (fluctuating moods, tiredness) were identified as the most sensitive endpoint. The effects were already observed with an oral dose of 2.5 mg/person (equivalent to 0.036 mg/kg bw based on an assumed body weight of 70 kg) – both following one-time (Ballard and de Wit 2011) and repeated intake (Beal et al. 1995; Beal et al. 1997). This dose therefore represented the LOAEL (lowest-observed adverse effect level). Using an uncertainty factor of 30 (factor of 3 for extrapolation from a LOAEL to a NOAEL, factor of 10 for inter-individual fluctuations), EFSA derived an ARfD of 0.001 mg Δ9-THC/kg bw.

In addition, endpoints of the subchronic and chronic study section of the NTP Study (1996) were evaluated and the extension of the oestrus cycle in rats was identified as the most sensitive endpoint during the subchronic study. The authors refrained from deriving a TDI, as the BMDL10 of 0.73 mg Δ9-THC/kg bw for this effect was more than 700 times greater than the ARfD and compliance with the ARfD was therefore also seen as protective in the case of chronic intake (EFSA 2015).

3.1.4.2 Hazard potential of Δ9-THC

The following summary on the hazard potential of Δ9-THC is mainly based on the EFSA Opinion from 2015 and studies cited therein. We refer readers to this opinion for a detailed description of all relevant studies.

Toxicokinetics

Δ9-THC is well absorbed following oral intake (90-95 %) due to its high lipophilicity. Systemic bioavailability following oral intake is very low, however, and subject to major fluctuation. The figures for oral bioavailability range from 6 to 20 %. Inhalation of Δ9-THC sometimes leads to far higher levels of bioavailability, although there are major fluctuations. The low oral bioavailability is due to a partial degradation of Δ9-THC in the acidic conditions found in the stomach and extensive first-pass metabolism in the liver (FDA 2004; Huestis 2007). A model using mice also showed active export via P-glycoprotein, and this can also reduce systemic bioavailability following oral intake (Bonhomme-Faivre et al. 2008).

Maximum plasma levels of Δ9-THC are reached after roughly 2 hours (h) following oral intake. Δ9-THC is subject to rapid and pronounced tissue distribution. Depending on the estimate, the distribution volume is in the order of 3 or 10 l/kg bw. Binding to plasma proteins (95-99 %) is pronounced. Due to its high lipophilicity, Δ9-THC accumulates in the fatty tissue and is released from this tissue over a long term. The initial plasma half-life of Δ9-THC is approx. 4 h, while the terminal plasma half-life fluctuates between 25 and 36 h. Δ9-THC crosses the placenta (FDA 2004; Huestis 2007).

In the liver, Δ9-THC is mainly converted via the cytochrome-P450 (CYP) enzymes CYP2C9, CYP2C19 and CYP3A4 into the active metabolite 11-hydroxy-Δ9-THC, which in turn is converted into the inactive metabolite 11-nor-9-carboxy-Δ9-THC by oxidation. Moreover, the mother substance and both metabolites can be glucuronidated. Various further minor metabolites are described in the scientific literature (FDA 2004; Huestis 2007). Other cannabinoids of the hemp plant can influence the metabolism of Δ9-THC (Stout and Cimino 2014). To date, metabolic conversion of Δ9-THCA-A into Δ9-THC has not been observed either in rats (Jung et al. 2009) or humans (Wohlfahrt 2012).

Polymorphisms in the relevant CYP enzymes can therefore have a significant influence on the degradation of Δ9-THC. Sachse-Seeboth et al. (2009), for example, observed following the same oral dose a threefold higher plasma level curve of Δ9-THC as well as stronger sedation in volunteers with CYP2C9*3/*3 gene status compared to volunteers with CYP2C9*1/*1 gene status.

Excretion of Δ9-THC and its metabolites is mainly via faeces and to a lesser extent via urine. The compounds are subject to a pronounced enterohepatic circulation. Accumulation in – and slow release from – the fatty tissue results in a long terminal elimination half-life (FDA 2004; Huestis 2007). The latter phenomenon is also responsible for the fact that the primary metabolite 11-nor-9-carboxy-Δ9-THC can still be detected in the urine several months after the last cannabis consumption in people who frequently consume cannabis and in whose fatty tissue the substances have therefore accumulated (Lowe et al. 2009).

Mechanism of action

Effects of Δ9-THC are primarily due to binding as a partial agonist to the cannabinoid receptors CBR1 and CBR2 of the endocannabinoid system. CB1 receptors are present above all in the central nervous system but also on peripheral neurons, endocrine glands, lymphocytes, heart muscle cells and various other tissues. CB2 receptors, on the other hand, are mainly localised on cells of the immune system. The receptors are primarily presynaptic and modulate the release of various neurotransmitters. This enables direct action in different target organs. Frequent exposure to Δ9-THC can lead to a decrease in the number of cannabinoid receptors, leading in turn to the development of tolerance (Marquardt and Schäfer 2004; Pertwee 2008). As receptors in the area of the hypothalamus are activated, endocrine effects are also possible due to influence of the hypothalamus-hypophysis end organ axis. These effects include modified production of sex hormones, prolactin, growth hormones and thyroid hormones (Brown and Dobs 2002).

The effects of Δ9-THC in different individuals may be influenced by polymorphisms of the cannabinoid receptor genes CNR1 and CNR2 (Onaivi 2009) or other genes involved in the endocannabinoid system or neurotransmitter metabolism, such as those for fatty acid amide hydrolase (FAAH) (Tyndale et al. 2007) or catechol-O-methyltransferase (COMT) (Estrada et al. 2011; Pelayo-Teran et al. 2010).

Interactions of Δ9-THC with the opioid system have also been discussed (Vaysse et al. 1987). Moreover, studies have recently been conducted on epigenetic effects of Δ9-THC (Sido et al. 2015; Watson et al. 2015; Yang et al. 2014).

3.1.4.3 Findings on toxicity from animal studies

Acute toxicity

The acute toxicity of Δ9-THC is low. The mean lethal dose (LD50) following oral intake is 666 mg/kg bw in rats and 482 mg/kg bw in mice (Phillips et al. 1971). A one-time oral dose of 3,000 mg/kg bw in dogs or 9,000 mg/kg bw in monkeys was shown not to be lethal (Thompson et al. 1973).

Subchronic toxicity

In the context of the National Toxicology Program (NTP), rats and mice (10 male and female animals in each case) were treated orally over a period of 90 days with up to 500 mg Δ9-THC/kg bw and day (treatment on 5 days a week). The following effects were most commonly observed in rats: increased mortality (in the highest dose group), reduced body weight, effects on the nervous system (aggressiveness, lethargy, sensitivity to touch, cramps), diarrhoea, reduced epididymis weight, testicular atrophy, reduced sperm motility, increase in abnormal sperm, reduced uterus weight, uterus atrophy and hypoplasia of the ovaries as well as prolongation of the oestrus cycle. The most frequently observed effects in mice were reduced body weight, effects on the nervous system (aggressiveness, lethargy, cramps), reduced sperm concentration, reduced uterus weight and prolongation of the oestrus cycle (NTP 1996).

Chronic toxicity

In the context of the NTP, rats and mice (60-80 male and female animals in each case) were treated orally over a period of two years with up to 50 or 500 mg Δ9-THC/kg bw and day (treatment on 5 days a week). The following effects were most commonly observed in rats: reduced body weight and effects on the nervous system (cramps). An interim analysis after 15 months also determined the following effects: higher leukocytes and lymphocytes, reduction in blood platelets, reduction in the relative weight of the thymus and an increase in the follicle-stimulating hormone (FSH) and the luteinising hormone (LH). The most frequently observed effects in mice were reduced body weight, effects on the nervous system (hyperactivity, cramps), increased incidence of hyperplasia of the thyroid follicular cells, and an increase in the incidence of hyperplasia and ulcerations of the forestomach. An interim analysis after 15 months also determined the following effects: higher leukocyte and lymphocyte counts (NTP 1996).

Carcinogenicity

In the context of the NTP, rats and mice (60-80 male and female animals in each case) were treated orally over a period of two years with up to 50 or 500 mg Δ9-THC/kg bw and day (treatment on 5 days a week). The NTP assessed an increased incidence of adenomas of thyroid follicular cells as equivocal evidence of carcinogenic activity. However, this finding occurred in mice in isolated cases at the mean dose of 125 mg/kg bw and did not indicate any dose-dependency. Malignant tissue changes were not observed (NTP 1996).

Genotoxicity

Under certain conditions, individual in vitro studies (sister chromatid exchange, comet test, micronucleus test) provided indications of DNA-damaging potential of Δ9-THC (Koller et al. 2013; NTP 1996; Parolini and Binelli 2014). In contrast, a bacterial mutagenicity test, an in vitro chromosome aberration test and an in vivo micronucleus test in mice treated orally with up to 500 mg Δ9-THC/kg bw and day over a period of 13 weeks (on 5 days a week) showed no signs of genotoxic activity (NTP 1996). In conclusion, the available data do not indicate a genotoxic potential of Δ9-THC in vivo.

Reproductive toxicology

Reproductive toxicology studies with Δ9-THC administered to mice and rats did not indicate a teratogenic potential. What was observed, however, were reduced weight of the mother animals, lower litter size and an increase in foetal mortality or early resorptions. These effects were dose-dependent and correlated with toxicity in the mother animals (FDA 2004). There are also some findings from studies of subchronic and chronic toxicity (prolongation of the oestrus cycle, reduced sperm quality etc.) that point to a negative influence of Δ9-THC on reproductive capability (NTP 1996).

Neurotoxicity

Studies using Δ9-THC in mice and rats observed numerous neurotoxic effects. Alongside functional changes – affecting for example locomotor activity and social behaviour as well as learning and memory – also neurophysiological changes on the molecular level were observed. These types of change were reported following both one-time and repeated exposure to Δ9-THC. It should also be noted that effects were not only observed in temporal connection with exposure but sometimes also persisted beyond the period of exposure. Neurological changes were, for example, observed in adult animals exposed perinatally to Δ9-THC (Abdel-Salam et al. 2013; Amal et al. 2010; Butovsky et al. 2005; Campolongo et al. 2007; Harte and Dow-Edwards 2010; Katsidoni et al. 2013; Newsom and Kelly 2008; Senn et al. 2008; Tselnicker et al. 2007; Whitlow et al. 2003; Wu and French 2000). Moreover, Δ9-THC can reinforce the neurotoxic effects of other compounds such as ethanol (Hansen et al. 2008). In the developmental phase, the brain reacts more sensitively to Δ9-THC than the brain of adult animals (Downer et al. 2007).

Immunotoxicity

Immunomodulating effects of Δ9-THC are described in literature. One finding that was observed in mice following intake of Δ9-THC was a reduced number of different cell types of the immune system (Do et al. 2004; Karmaus et al. 2013; Lombard et al. 2011). In mice, the immune response to an infection with influenza virus was reduced following intake of Δ9-THC (Karmaus et al. 2013). After administration of Δ9-THC to pregnant mice, Lombard et al. (2011) observed an immunosuppressive effect in foetuses, and this effect persisted following birth. The effects on the immune system are at least partly mediated via CB1 and CB2 receptors (Karmaus et al. 2013; Lombard et al. 2011).

Relevant human data

Health-related consequences of cannabis consumption have been intensively investigated in the past. Many studies focused on inhalative exposure, as cannabis preparations used to induce intoxication are commonly smoked. However, human studies with oral exposure to Δ9-THC are more suitable for the assessment of the hazard potential of Δ9-THC as an ingredient in foods. Studies of this kind are mainly found in the pharmaceutical sector, as preparations of *Cannabis sativa* L. or Dronabinol (in other words, synthetic Δ9-THC) are also used for medicinal purposes, and the preparations used for these purposes are generally taken orally. Δ9-THC is currently used for a range of indications, in particular in the treatment of cytostatic-induced nausea and vomiting as well as to increase the appetite of AIDS patients.

Data are available from various clinical studies that investigated the pharmacological effects of Δ9-THC following the oral intake in different patient collectives. The most important studies with Δ9-THC are described in detail in the EFSA opinion (2015). It should be noted that the clinical studies and the doses used were primarily designed to investigate the pharmacological effects on different illnesses. As undesired effects were already observed in individual cases at the lowest dose of 2.5 mg/day (Beal et al. 1995; Beal et al. 1997; Struwe et al. 1993), it was not possible to derive a NOAEL.

Some studies with Δ9-THC were performed on healthy volunteers, and here again the lowest investigated dose was 2.5 mg Δ9-THC. Moderate effects were already observed with this dose (Ballard and de Wit 2011). Consequently, it is not possible to derive a NOAEL in this case either. It should be noted that most of the studies on healthy volunteers involved people who had already consumed cannabis in the past (Ballard and de Wit 2011; Chesher et al. 1990). It is conceivable that these people had built up a tolerance and therefore reacted less sensitively to the intake of Δ9-THC than volunteers who have no previous experience with cannabis.

Summary of assessment of the hazard potential of Δ9-THC

The ARfD of 0,001 mg Δ9-THC/kg bw recently derived by EFSA is based on a LOAEL of 2.5 mg Δ9-THC/kg bw (equivalent to 0.036 mg/kg bw based on the assumption of a body weight of 70 kg) and a safety factor of 30 to allow for inter-individual variability as well as the extrapolation from LOAEL to NOAEL. This LOAEL was identified in multiple studies – both following one-time intake by healthy volunteers and repeated intake within the context of clinical studies. The effects occurring at this dose level primarily involved the central nervous system and were moderate in nature (EFSA 2015).

The recommendation not to exceed a maximum intake of 0.001-0.002 mg Δ9-THC/kg bw published by the BgVV in 1997 is also based on a LOAEL of 2.5 mg Δ9-THC/kg bw (equivalent to 0.040 mg/kg bw assuming a body weight of 60 kg) identified in a human study and a safety factor of 20-40 to take account of open scientific questions (BgVV 1997). The current derivation of the ARfD is therefore in line with the earlier recommendations of the BgVV. The BfR supports the ARfD recently defined by EFSA and considers this level as being protective – both for acute and chronic exposure to Δ9-THC from foods.

3.1.5 Exposure

3.1.5.1 Foods containing hemp that are commercially available in Germany

A search was performed with the help of the MINTEL database (MINTEL 2016) to identify relevant food groups in the German market. This database includes information on foods and their ingredients as listed on the packaging. A search for products containing hemp showed that a total of 202 hemp-containing foods were brought onto the German market in the period from 2012 to 2017. 50 of these products are classed as food supplements mainly containing protein powder made from hemp seeds. The remaining 152 products fall into a diverse range of food groups in which hemp-containing foods occur (see Figure 2). The main ingredient in the products is hemp seeds or the protein or oil obtained from hemp seeds. Tea varieties are the exception, as these tea products are based on hemp leaves or hemp flowers.

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Based on the MINTEL data, snacks containing hemp (e.g. hemp snacks covered in chocolate), muesli bars and energy bars (e.g. fruit bars with hemp seeds) are the group of products found most frequently in the German market, accounting for 22 % of the total. They are followed by breakfast cereals with 10 % (e.g. muesli with hemp seeds) and other beverages with 8 % (e.g. hemp milk, beer with hemp oil). The products accounting for 7 % of the total results in MINTEL include pasta sauces – above all pesto, which contains hemp seeds alongside other ingredients like spinach or tomatoes. The sandwich spreads are also marketed as vegan products with hemp seeds together with tomatoes, courgettes or peanuts in the form of a paste.

Further hemp-containing products in MINTEL with a share of 5 % include desserts with a hemp seed basis together with fruit or chocolate. Then there are also baking ingredients such as special hemp flour or direct baking mixes made of hemp seed as a gluten-free alternative for baking bread. The other foods include such things as cheese made from hemp milk.

Legend (pie chart):
- Snacks/Müsli-Riegel/Energy-Riegel
- Frühstückscerealien
- Sonstige Getränke
- Pastasoßen
- Herzhafte Gemüsepâtés/Aufstriche
- Salzgebäck
- Öl
- Schokoladentafeln
- Tee
- Desserts aus dem Kühlfach
- Backzutaten & Backmischungen
- Energy-Getränke
- Andere Soßen und Gewürze
- Salatsoßen, Essig und Mayonnaise
- Sonstige Lebensmittel
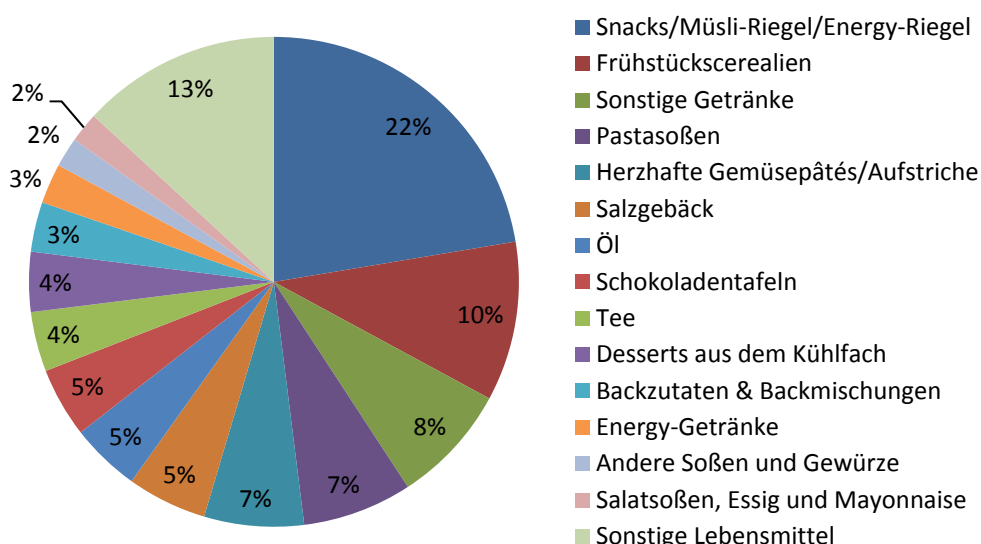
Snacks/Muesli bars/Energy bars
Breakfast cereals
Other beverages
Pasta sauces
Savoury vegetable pates/Sandwich spreads
Savoury snacks
Oil
Bars of chocolate
Tea
Desserts from refrigerated shelves
Baking ingredients & baking mixes
Energy drinks
Other sauces and spices
Salad dressings, vinegar and mayonnaise
Other foods

Figure 2: The wide variety of hemp-containing foods on the German market based on novel products in the MINTEL database 2012-2017, full text search "% hemp".

It should be taken into account that this overview only includes foods that have been brought onto the German market since 2012 but does not cover foods that were already being marketed at that time. This MINTEL-based overview therefore supplies a basic overview of the variety of hemp-containing foods that are on the market in Germany but does not provide an exhaustive picture of the market situation.

3.1.5.2 Consumption data

No consumption data are available for foods containing hemp. The consumption data used in this opinion are therefore confined to analogous food categories to which the various hemp-containing foods would be assigned.

The data from the two independent 24 h *recalls* of the NVS II study collected in a computer-assisted interview using "EPIC-SOFT" (Krems *et al.* 2006; MRI 2008) were used as a data basis for consumption for the adult German population. The data of 13,926 persons for whom both interviews were available were evaluated. Due to the presence of consumption data on individual days, the method of the 24 h *recalls* is suitable for exposure assessment with regard to both acute and chronic risks.

The evaluations for the children are based on the data from the VELS study (Banasiak *et al.* 2005; Heseker *et al.* 2003). The VELS study was conducted between 2001 and 2002 with 816 infants and small children between the ages of 6 months and less than 5 years of age throughout Germany. The intake calculations used here are based on the data for small children between the ages of 2 to less than 5. For each child, the parents kept two 3-day nutrition logs covering all consumed foods. These intake calculations use the consumption data of the children relative to their individual body weight. Due to the presence of consumption data on individual days, the 2x3 nutrition logs are suitable for exposure assessment with regard to both acute and chronic risks.

3.1.5.3   General aspects of exposure assessment within the context of this opinion

As there are no consumption data for foods containing hemp, it is not possible to conduct an exposure assessment in the classical sense. Therefore, for the examination of the acute intake of total Δ^9-THC the consumtion was determined that would result in intake levels equivalent to the ARfD of 0.001 mg/kg bw for Δ^9-THC. For the latter calculation, the total Δ^9-THC content was considered, on the one hand as being equivalent to the respective guidance values of the BgVV (for assessment of the protective level of the guidance values) and, on the other, equivalent to the recently measured data on levels contained (for assessment of the current potential exposure of consumers). It was assumed that the quantities of consumed hemp-containing foods are equivalent to those of other foods in the same food category. Based on this assumption,the real actute consumption for adults and children estimated from NVS II and VELS is compared to the derived theorectical consumption that would result in tapping the full potential of the ARfD. The data being considered here do not include the consumption for food supplements by either adults or children that could be used for the purpose of comparison. In the case of food supplements, however, it is generally possible to determine exposure in individual cases based on the recommended daily intakes that have to be declared on the packaging or the accompanying information leaflet.

In view of the analytical uncertainties discussed in section 3.2.2 with regard to the quantification of total Δ^9-THC or the individual analytes Δ^9-THC and Δ^9-THCA-A, and due to the possible conversion of Δ^9-THCA-A into Δ^9-THC, the parameter "total Δ^9-THC" is used for exposure assessment.

3.1.5.4   Considerations onexposure when the guidance value of the BgVV were reached

Based on the assumption that hemp-containing foods exhibit the guidance values of the BgVV for total Δ^9-THC, the theoretical consumption of these foods were calculated for children and adults at which the ARfD would be reached (see Figures 3 and 4). These quantities are compared to the consumption of analogous foods determined using the data from the NVS II and VELS studies. The assessment of "non-alcoholic and alcoholic beverages", is limited to consumption of herbal tea – based on the high total Δ^9-THC levels in hemp tea, which mainly consists of leaves of the hemp plant and is therefore comparable with herbal tea in the broadest sense. For hemp oil, consumption data for edible oils were considered that are usually used in a similar way (e.g. olive oil, pumpkin seed oil, walnut oil) that are not heated. In the last group – "all other foods" – the 95th percentile of the individual totals was calculated for the foods listed under this heading in Figure 5.

Accordingly, adults would tap the full potential of the ARfD with total Δ^9-THC levels at the level of the guidance values if they drink 14 litres of non-alcoholic and alcoholic beverages. By way of comparison, the actual acute consumption quantities for herbal tea as an analogon for hemp tea are in the order of 1.3 litres (P95). In the case of hemp oil, consumption of 14 ml would result in values that reach the ARfD. The actual short-term high consumption of similar oils is twice as high in adults at 28.5 ml, however. For all other foods containing hemp, the consumption quantity that would result in fully utilising the ARfD in adults is 467 g. By way of comparison, the consumption data for the sum of the foods in the BgVV group for "all other foods" show a higher analogous consumption of 620 g.

Food groups with guidance values of the BgVV for total Δ^9-THC	Guidance values	Theoretical consumption quantity until the ARfD (0.001 mg/kg bw/d) is reached		Real consumption quantity of analogous foods (P95, consumers only)		
	mg/kg	g/d or ml/d	g/d or ml/d per kg bw[1]	% consumers[2]	g/d or ml/d	g/d or ml/d per kg bw[3]
Non-alcoholic and alcoholic beverages	0.005	**14,000**	200,0	22*	**1,300.0***	27.00*
Edible oils	5	**14**	0,2	33	**28.5**	0.40
All other foods	0.15	**466.7**	6,7	95	**620**	8.76

Figure 3: Calculation of consumption for adults based on the guidance values of the BgVV. Calculation of the theoretical consumption quantity that would be necessary based on the guidance values of the BgVV to reach the ARfD for Δ^9-THC and comparison of the real consumption quantity of analogous foods determined within the context of the NVS II study for adults;[1] Standard body weight of 70 kg; [2] The percentage of consumers of analogous hemp-containing foods is probably far lower, but this likely does not have any relevant influence on the

quantities consumed on a single day; [3] individual body weights; * Refers exclusively to consumption of herbal tea; assumption: carryover of total Δ^9-THC into the beverage = 100 %.

Due to the lower body weight of children, the absolute consumption quantities that cause to reach the ARfD are well below those for adults in the case of total Δ^9-THC levels at the level of the guidance values. The consumption of 3.2 litres of hemp-containing beverages, 3.2 ml of hemp oil or 108 g of other hemp-containing foods leads to tap the full potential of the ARfD in children. In comparison, the actual acute consumption of herbal tea as an analogon for hemp tea is lower at approximately 900 ml – but it is significantly higher in the case of edible oils (17.4 ml) and all other foods (518.5 g) (see Figure 4).

Food groups with guidance values of the BgVV for total Δ^9-THC	Guidance values	Theoretical consumption quantity until the ARfD (0.001mg/kg bw/d) is reached		Real consumption quantity of analogous foods (P95, consumers only)		
	mg/kg	g/d or ml/d	g/d or ml/d per kg bw[1]	% consumers[2]	g/d or ml/d	g/d or ml/d per kg bw[3]
Non-alcoholic and alcoholic beverages	0.005	**3,230.0**	200.0	29*	**899.0***	59,.3*
Edible oils	5	**3.2**	0.2	66	**17.4**	1.07
All other foods	0.15	**107.7**	6.7	100	**518.5**	31.79

Figure 4: Calculation of consumption for children based on the guidance values of the BgVV. Calculation of the theoretical consumption quantity that would be necessary based on the guidance values of the BgVV to reach the ARfD for Δ^9-THC and comparison with the real consumption quantity of analogous foods determined within the context of the VELS study for children;[1] Standard body weight of 16.15 kg; [2] The percentage of consumers of analogous hemp-containing foods is probably far lower, but this likely does not have any relevant influence on the quantities consumed on a single day [3] individual body weights; * Refers exclusively to consumption of herbal tea; assumption: carryover of total Δ^9-THC into the beverage = 100 %.

3.1.5.5 Data on total Δ^9-THC levels from official food monitoring activities

In order to assess the current data situation with regard to total Δ^9-THC in foods, the German federal states (*"Bundesländer"*) were requested via the Federal Office of Consumer Protection and Food Safety (BVL) for data on Δ^9-THC levels in foods. The BfR was subsequently provided with data for the years from 2007 to 2016 as individual data for 261 data sets based on 210 samples. A major part of the data (n=210) refers to Δ^9-THC, followed by Δ^9-THCA-A (n=44) and total Δ^9-THC (n=7). Due to the analytical challenges in terms of the selective quantification of Δ^9-THC and the possible conversion of Δ^9-THCA-A into the toxicologically relevant Δ^9-THC, evaluation of all the various parameters was performed together under the designation "total Δ^9-THC". The data comprised data from 228 routine samples, 24 suspect/follow-up and complaint samples, one monitoring project sample and eight samples taken for other reasons. As the data on levels contained were used for an acute intake assessment, no differentiation was made for the current evaluation with regard to the reasons for sampling.

Values below the limit of detection and limit of quantification (LOD/LOQ) were taken into account using the three approaches of modified lower bound, medium bound and upper bound. In the modified lower bound, values below the limit of detection are set to zero and values below the limit of quantification are set to the limit of detection. Where there was no information on the limit of detection, the corresponding value was also set to zero. The medium bound takes account of the values below the LOD/LOQ by using half the value of the respective LOD/LOQ. In the upper bound approach, the values below the LOD/LOQ are set to the respective LOD/LOQ.

Figure 5 shows the data for total Δ^9-THC levels in the food groups listed by the BgVV as well as, where applicable, the "assigned" foods and specifies the percentage of samples that exceed the respective guidance values of the BgVV. Food supplements are listed separately due to their special status. The levels in tea and coffee were measured in the powder and converted to figures representing the ready-to-drink beverage for the purposes of this evaluation. To this end, it was assumed that 100 % of the total Δ^9-THC is transferred into the beverage and that 2 g of tea make an infusion of 200 ml (factor 0.01) and 8 g of coffee powder make a 160 ml coffee beverage (factor 0.05) (EFSA 2012). The BfR is of the opinion that the assumption of 100 % carryover is justified, as experimental data on the carryover point to high fluctuations (see section 3.2.2). The group of non-alcoholic and alcoholic beverages contains levels of total Δ^9-THC in tea and tea-like products such as hemp-leaf tea and herbal tea. Here, the values in the 95th percentile (medium bound) are in the order of 1.41 mg/kg total Δ^9-THC in the infusion. In addition, this group also includes three samples of coffee, but all of these samples remained below the limit of detection and limit of quantification. Moreover, alcohol-free beverages (beverages containing hemp, iced tea, energy/fitness drinks showed a total Δ^9-THC level of 0.02 mg/kg (95th percentile, medium bound). The beers and beer-like beverages show a far lower total Δ^9-THC content of 0.003 mg/kg (95th percentile, medium bound). Only one value was measured for wine-like beverages (wine made from honey), but the value was below the LOD/LOQ. There was also a very small number of samples (n=2) for spirits (vodka, liqueur from other herbs/spices/flowers), which showed a total Δ^9-THC content of 0.21 mg/kg (95th percentile, medium bound). This means that, with the exception of the beers, between 22 % and 100 % of the samples of all drinks exceeded the total Δ^9-THC guidance value of 0.005 mg/kg. The food group "all other foods" contains a wide variety of different hemp-containing foods. These include the base products "hemp seeds", which have a comparatively high total Δ^9-THC level of 7.4 mg/kg (95th percentile, medium bound). The other values listed in Figure 5 are the result of very low sample numbers and do not permit any statements on the total Δ^9-THC levels of the foods in these individual groups that are actually available in the German market. Only one sample each is available for leafy vegetables (dried), sausage products (knackwurst and pre-cooked sausages), sweets, pesto and milk, for example. With regard to the "milk" sample, the data from the monitoring project do not exactly specify the type of milk. It is assumed that the milk in question is a milk imitation – in other words, hemp milk – which has a total Δ^9-THC content of 0.1 mg/kg. The total Δ^9-THC guidance values are exceeded by hemp seeds (75 %), leafy vegetables (100 %), fine pastries (50 %), baking/bread mixes (33 %), sandwich spreads (50 %) and pesto (100 %). Very high total Δ^9-THC levels of 1,230 mg/kg (95th percentile, medium bound) are found in hemp-containing food supplements, and nearly all samples (94 %) exceed the guidance value of 0.15 mg/kg.

Food groups and foods	N	Samples with levels below the LOD/LOQ [%]	Modified lower bound[1]			Medium bound[2]			Upper bound[3]			Samples with levels above the guidance values of the BgVV [%]
			P50	P95 [mg/kg]	Max	P50	P95 [mg/kg]	Max	P50	P95 [mg/kg]	Max	
Non-alcoholic and alcoholic beverages*	87	58	0	0.66	5.88	0.001	**0.66**	5.88	0.003	0.66	5.88	**38**
Tea varieties and tea-like products *	23	9	0.17	1.41	5.88	0.17	**1.41**	5.88	0.17	1.41	5.88	**87**
Coffee*	3	100	0	0	0	0.001	**0.001**	0.001	0.001	0.001	0.001	**0**
Non-alcoholic beverages	50	74	0	0.02	0.08	< 0.001	**0.02**	0.08	0.001	0.02	0.10	**22**
Beer, beer-like beverages	8	75	0	0.003	0.003	< 0.001	**0.003**	0.003	0.001	0.003	0.003	**0**
Wine-like beverages	1	100	0	0	0	0.03	**0.03**	0.03	0.05	0.05	0.05	**100**
Spirits	2	50	0.1	0.21	0.21	0.21	**0.21**	0.21	0.21	0.21	0.21	**50**

Edible oils (hemp oil)	55	20	2.0	47.0	232.8	2.0	**47.0**	232.8	2.6	47.0	232.8	**35**
All other foods	102	9	0.29	4.05	105.0	0.29	**4.05**	105.0	0.29	4.05	105.0	**61**
Hemp seeds	72	1	0.5	7.4	105.0	0.5	**7.4**	105.0	0.5	7.4	105.0	**75**
Leaf vegetables, dried	1	0	2.9	2.9	2.9	2.9	**2.9**	2.9	2.9	2.9	2.9	**100**
Bread and biscuits	2	0	0.05	0.07	0.07	0.05	**0.07**	0.07	0.05	0.07	0.07	**0**
Fine pastries	8	0	0.18	0.55	0.55	0.18	**0.55**	0.55	0.18	0.55	0.55	**50**
Cereal products, baking/bread mix**	3	0	0.09	0.24	0.24	0.09	**0.24**	0.24	0.09	0.24	0.24	**33**
Sausage products	1	0	0.04	0.04	0.04	0.04	**0.04**	0.04	0.04	0.04	0.04	**0**
Milk	1	0	0.10	0.10	0.10	0.10	**0.10**	0.10	0.10	0.10	0.10	**0**
Dairy products	4	75	0	< 0.001	< 0.001	< 0.001	**< 0.001**	< 0.001	< 0.001	< 0.001	< 0.001	**0**
Sandwich spread	2	0	0.23	0.39	0.39	0.23	**0.39**	0.39	0.23	0.39	0.39	**50**
Chocolates	4	50	0.07	0.14	0.14	0.07	**0.14**	0.14	0.10	0.14	0.14	**0**
Sweets	1	100	0	0	0	0.01	**0.01**	0.01	0.02	0.02	0.02	**0**

Ready meal	2	100	0	0	0	0.004	**0.004**	0.004	0.007	0.007	0.007	**0**
Pesto	1	0	11.2	11.2	11.2	11.2	**11.2**	11.2	11.2	11.2	11.2	**100**
Food supplements	17	0	1.14	1230.0	1230.0	1.14	**1230.0**	1230.0	1.14	1230.0	1230.0	**94**

Figure 5: Concentrations of total Δ^9-THC in food groups and foods (BVL, 2007-2016). The available data for total Δ^9-THC levels are shown for the food groups defined by the BgVV and, where applicable, for foods belonging to these food groups. In addition, the figure shows the underlying sample size, the percentage of samples with levels below the LOD/LOQ, and the percentage of samples with levels above the existing guidance values of the BgVV of 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. The 95th percentile of the medium bound is used as a basis for comparison. [1] Values < LOD= 0 and values < LOQ = LOD; [2] Values < LOD/LOQ = ½ LOD/LOQ; [3] Values < LOD/LOQ = LOD/LOQ; * Assumption of 100 % carryover in the case of tea and coffee; ** Dry product.

3.1.5.6 Considerations on exposure based on data on the levels contained in Δ^9-THC

Substitute foods were selected in order to estimate the possible exposure to total Δ^9-THC through the consumption of foods containing hemp. Based on the levels measured in monitoring in the 95th percentile, consumption quantities were calculated for these foods which would lead to tap the full potential of of the ARfD. For the BgVV group of non-alcoholic and alcoholic beverages, hemp tea was selected as the substitute food due to the high levels it contains (see Figure 5). The data for hemp oil was used for edible oils.

Food	Levels of total Δ^9-THC [mg/kg; medium bound; P95]	Theoretical consumption quantity until the ARfD is reached (0.001mg/kg bw/d)		Real consumption quantity of analogous foods (P95, consumers only)		
		g/d or ml/d	g/d or ml/d per kg bw[1]	% consumers[2]	g/d or ml/d	g/d or ml/d per kg bw[3]
Non-alcoholic and alcoholic beverages						
Hemp tea	1.41	**49.6**	0.71	22	**1300.0**	27.00
Edible oils						
Hemp oil	47	**1.5**	0.02	33	**28.5**	0.40
All other foods						
Pasta	n. a.	**n. a.**	n. a.	35	**340**	4.59
Hemp seeds	7.4	**9.5**	0.14	1	**95.0**	1.10
Bread, rolls	0.07	**1000.0**	14.29	87	**316.0**	4.33
Savoury snacks, crackers	n. a.	**n. a.**	n. a.	1	**200.0**	2.48
Biscuits	0.55	**127.3**	1.82	11	**100.0**	1.44
Muesli, cereal flakes	n. a.	**n. a.**	n. a.	13	**150.0**	1.94
Muesli bars	n. a.	**n. a.**	n. a.	2	**114.0**	1.49
Dessert (yoghurt, pudding)	0.001	**70000.0**	1000.00	37	**391.4**	5.26
Hemp milk	0.1	**700.0**	10.00	1	**912.5**	8.80

Figure 6: Determination of consumption by adults based on the data on contained levels established by official food monitoring schemes. [1] Standard body weight of 70 kg; [2] Although the percentage of consumers of analogous hemp-containing foods is presumably much lower, this presumably has no relevant influence on the quantities consumed in a single day. [3] Individual body weights; n.a. = not available.

A broader selection of substitute foods was made for the BgVV group of all other foods considering three criteria: 1. conspicuous levels contained, 2. frequent occurrence of product novelties in the MINTEL database and 3. expectation of high consumption. Accordingly, pasta (noodles), hemp seeds, bread and rolls, savoury snacks, biscuits, muesli and muesli

bars, as well as desserts with hemp and hemp milk, were considered here. As can be seen in Figure 6, consumption of only 50 ml of hemp tea result in 100 % tapping the full potential of the ARfD in adults due to the high total Δ^9-THC levels. At 1.3 litres, however, the actual acute consumption (P95) for herbal tea as an analogon is significantly higher. For hemp oil, a theoretical consumption of 1.5 ml results in a tapping the full potential of the ARfD on the basis of the total Δ^9-THC levels measured. In contrast the actual consumption (P95) of analogous edible oils is 28.5 ml. In the group "all other foods", most of the consumption estimated in NVS II lie below the consumption which lead to full tapping the full potential of the ARfD.

Food	Levels of total Δ^9-THC [mg/kg; medium bound; P95]	Theoretical consumption quantity until the ARfD is reached (0.001mg/kg bw/d)		Real consumption quantity of analogous foods (P95, consumers only)		
		g/d or ml/d	g/d or ml/d per kg bw[1]	% consumers[2]	g/d bzw. ml/d	g/d or ml/d per kg bw[3]
Non-alcoholic and alcoholic beverages						
Hemp tea	1.41	**11.5**	0.71	29	**899.0**	59.93
Edible oils						
Hemp oil	47	**0.3**	0.02	66	**17.4**	1.07
All other foods						
Pasta	n. a.	**n. a.**	n. a.	25	**220.0**	12.65
Hemp seeds	7.4	**2.2**	0.14	23	**15.0**	0.82
Bread, rolls	0.07	**230.7**	14.29	99	**166.0**	9.92
Savoury snacks, crackers	n. a.	**n. a.**	n. a.	24	**42.0**	2.82
Biscuits	0.55	**29.4**	1.82	40	**60.0**	3.76
Muesli, cereal flakes	n. a.	**n. a.**	n. a.	12	**109.0**	7.71
Muesli bars	n. a.	**n. a.**	n. a.	6	**60.0**	3.93
Dessert (yoghurt, pudding)	0.001	**16150.0**	1000.00	75	**350.0**	20.85
Hemp milk	0.1	**161.5**	10.00	1	**750.0**	57.25

Figure 7: Determination of consumption by children based on data on levels contained in food established by official food monitoring schemes. [1] Standard body weight of 16.15 kg; [2] Although the percentage of consumers of analogous hemp-containing foods is presumably much lower, this presumably has no relevant influence on the quantities consumed in a single day. [3] Individual body weights; n.a. = not available.

An exception here applies to hemp seeds, which are consumed by adults in analogous foods such as sunflower seeds or pine nuts in quantities amounting to 95 g (P95), and the ARfD is already utilised to the full with the consumption of 9.5 g. Hemp seeds are used as an

ingredient on the one hand, but can also be consumed directly in snacks. With children (Figure 7), the acute consumption quantity (95th percentile) of 900 ml of herbal tea is much greater than the consumption quantity of 12 ml at which the ARfD for hemp tea is already used up. Where hemp oil is concerned, consumption of analogous edible oils by children is 17.4 ml according to the VELS study. This consumption level is significantly above the theoretically permitted consumption quantity of 0.3 ml which would already result in full tapping the full potential of the ARfD. In the group "all other foods", the real consumption quantities of analogous foods lie above the theoretically permitted consumption quantities for hemp seeds, biscuits and hemp milk. With bread and rolls, the analogous consumption quantities are below the levels which would fully utilise the ARfD.

3.1.6   Risk characterisation

After an ARfD of 0.001 mg/kg bw for the oral uptake of Δ^9-THC has been derived by EFSA in 2015, it was the scope of this opinion to evaluate whether the guidance values published by the BgVV in 2000 for Δ^9-THC levels in ready-to-eat foods are still suitable from a toxicological point of view as a basis for . For this purpose, data on the consumption of hemp-containing foods would be required in addition to the toxicological reference point in the form of an ARfD. However, hemp-containing foods belong to the category of seldomly consumed foods, which is why corresponding consumption data were not available for adults or children. The consumption data used in this opinion is therefore restricted to analogous food categories (as outlined in section 3.1.5) to which the various hemp-containing foods would also have to be allocated. An exposure assessment in the classical sense was therefore not possible. Instead, possible health risks were estimated on the basis of model calculations.

In a first step, it was evaluated on the basis on actual consumption data whether the guidance values for maximum Δ^9-THC levels in food established in 2000are still suitable as a basis for the assessment from a toxicological point of view. This was conducted as follows:

1.   Under the assumption that foods containing hemp contain levels equivalent to the guidance values of the BgVV for Δ^9-THC, the theoretical consumption of these foods at which the ARfD would be reached were calculated for children and adults.

2.   Comparison of the theoretical consumption quantities with the real consumption quantities of analogous foods established on the basis of the data from the NVS II and VELS studies.

The individual calculations are shown in section 3.1.5.4. It has to be taken into account that the following evaluation is not based on a classical exposure assessment. Instead, the comparison scenario used is based on the assumption that the consumption of hemp-containing and analogous foods is the same. The comparison may therefore be flawed with an inaccuracy. It can be assumed, however, that the observed foods essentially differ from one another with regard to the frequency of consumption and percentage of consumers in the population, but also that they are comparable with regard to the one-off quantities consumed in one day. In this way, the uncertainties involved in a rough estimate of acute exposure are regarded as acceptable. This model calculation permits the best possible approximation of the issue in the view of the BfR. As acute toxicity in particular has to be considered in this evaluation, the data on levels contained as well as the consumption data in the 95th percentile (medium bound) have to be taken into account. The overall picture produces the following result:

a) Guidance value for non-alcoholic and alcoholic beverages

The assessment of the guidance value for non-alcoholic and alcoholic beverages was made entirely on the basis of the possible consumption of tea-like products containing hemp. Consumption data on herbal tea was used as a reference. It was shown that, considering tea with a Δ^9-THC level equivalent to the guidance value, the consumption quantity which would result in a Δ^9-THC-dose equivalent to the ARfD in adults (~ 14 l) as well as children (~ 3 l) is significantly greater than the actual consumption quantity of herbal tea (adults: ~ 1.3 l; children: ~ 0.9 l).

b) Guidance value for edible oils

For the assessment of the guidance value for edible oils the theoretical consumption of hemp oil was compared with the actual consumption of analogous edible oils. For hemp oil containing a Δ^9-THC level equivalent to the guidance value, the theoretical consumption of ~ 14 ml of hemp oil by adults and ~ 3 ml by children would be sufficient to ingest a Δ^9-THC dose equivalent to the ARfD. In comparison, the actual daily consumption quantity of analogous edible oils is considerably higher (adults: ~ 28.5 ml; children: ~ 17.4 ml). On the basis of these data and based on the assumption of a similar consumption of hemp-containing and analogous foods, an exceedance of the ARfD is regarded as likelyfor both adults and children solely through the consumption of hemp oil.

c) Guidance value for all other foods

A theoretically acceptable consumption of 467 g by adults and 108 g by children in this food category must be seen in relation to an actual consumption of analogous foods of 620 g by adults and 519 g by children. Therefore, also in this food category the actual consumption of analogous foods is higher than the theoretically permitted consumption at which the ARfD would be reached.

The model calculation shows that, at least among high consumers, the ARfD could be clearly exceeded through the consumption of individual foods. The exceedances in children which result from this comparison scenario are particularly prominent. On this basis, it has to be called into question whether the guidance values for Δ^9-THC levels in food published by the BgVV in 2000 are still suitable as a basis for assessment from a toxicological point of view.

In a second stage, considerations regarding exposure were made on the basis of real data on levels of total Δ^9-THC in foods containing hemp.

Data from official food monitoring indicate (see section 3.1.5.5) that even the existing BgVV guidance values for Δ^9-THC levels in hemp-containing foods are sometimes exceeded by far. For the food category of non-alcoholic and alcoholic beverages, the available data on Δ^9-THC levels primarily support the evaluation of tea-like products and alcohol-free drinks because of the sample size. Whereas an exceedance could only be observed in 22 % of the samples of alcohol-free beverages, and with a measured value of 0.02 mg/kg, the levels (P95, medium bound) lie only moderately above the existing guidance value of 0.005 mg/kg, an exceedance was seen for 87 % of the samples of tea-like products and the levels (P95, medium bound) were also much higher at 1.41 mg/kg. Also for hemp oilsthe sample size supports assessment of the levels they contain. In this case, 35 % of the samples show an exceedance of the guidance value, and with a measured value of 47 mg/kg (P95, medium

bound), the level found is significantly higher than the guidance value of 5 mg/kg. For all other foods, meaningful data are only available for hemp seeds, where 75 % of the samples exceed the existing guidance value and the measured value of 7.4 mg/kg (P95, medium bound) lies significantly above the guidance value of 0.15 mg/kg. Hemp-based food supplements have a special status, with 94 % of samples exceeding the existing guidance values and levels (P95, medium bound) exceedingly high at 1,230 mg/kg.

Due to a lack of consumption data on foods containing hemp, the estimation of possible health risks was made here too on the basis of a model calculation. In this case, the real data on Δ^9-THC levels was used to calculate the theoretical consumption quantity at which the ARfD would be reached.

Based on the data on levels contained, adults could to drink up to ~ 50 ml and children up to ~ 12 ml of hemp tea without exceeding the ARfD. This stands opposed to considerably higher intake quantities of the analogous food in the form of herbal tea (children: ~ 900 ml; adults: ~ 1300 ml). For hemp oil too, the theoretically permitted consumption quantity is significantly less for adults (~ 1.5 ml) as well as children (~ 0.3 ml) than the consumption quantity of analogous edible oils (adults: ~ 29 ml; children: ~ 17 ml). In the "all other foods" group, a theoretically permitted consumption quantity of 9.5 g of hemp seeds for adults and 2.2 g for children contrasts with a consumption quantity of analogous foods of 95 g (adults) and 15 g (children). No consumption data of any kind is available for food supplements, which had conspicuously high total Δ^9-THC levels, with the result that no general assessment can be made. Standard recommendations on daily consumption listed on the packaging or pack inserts of products of this kind are 1 g per day for some products, however, according to brief, non-representative research on the Internet. On the basis of the established levels, the model calculation shows exposure of more than 1 mg of total Δ^9-THC per person and day.

The model calculation shows that the ARfD is clearly exceeded, at least among high consumers of hemp-containing foods. Particularly prominent here too are the exceedances in children which result from this comparison scenario. In the opinion of the BfR, the consumption of hemp-containing foods with these levels of total Δ^9-THC can lead to an exceedance of the ARfD.

It is possible, in the view of the BfR, that doses of Δ^9-THC which lie within the range of medically used doses of ≥ 2.5 mg per person and day are ingested through the consumption of hemp-containing foods. Pharmacological effects must therefore be expected in cases of this kind. As the occurrence of psychomotor effects must also be expected with doses within this range (FDA 2004; Hänseler AG 2014), it is also possible that the consumption of hemp-containing foods can impair a person's aptitude and ability to drive a motorised vehicle or operate dangerous machinery. These psychomotor effects can be reinforced by the consumption of alcoholic beverages (Ballard and de Wit 2011; Chesher *et al.* 1976; Lukas and Orozco 2001) and certain drugs (FDA 2004; Hänseler AG 2014). The question therefore arises, in the view of the BfR, as to whether hemp-containing foods with correspondingly high Δ^9-THC levels – especially those which contain Δ^9-THC as an ingredient (leaves, flowers etc) – can still be regarded as food.

Other relevant aspects

As cannabinoids are usually not formed in the seeds of hemp plants, small quantities of Δ^9-THC that occur are regarded primarily as contamination caused by contact with other plant parts containing Δ^9-THC (Ross *et al.* 2000). It should therefore be possible, in the opinion of the BfR, to reduce the levels in the seeds of hemp plants and foods made from them by taking suitable procedural measures. By doing so, an exceedance of the guidance values in the corresponding hemp-containing foods and/or exceedance of the ARfD could generally be avoided.

With the exception of the seeds and roots, the entire hemp plant is covered with glandular hairs which produce a cannabinoid-containing resin (Lachenmeier 2004). With hemp-containing tea-like products consisting especially of hemp leaves and hemp flowers, Δ^9-THC is therefore an ingredient. The Δ^9-THC level is subject to great fluctuations, depending on the hemp species and various environmental factors. In the view of the BfR, it is doubtful whether the levels in foods of this kind can be lowered reliably in order to avoid an exceedance of the guidance values and/or ARfD in the corresponding hemp-containing foods.

According to the world drug report by the United Nations' Office of Drugs and Crime, around 180 million people all over the world aged between 15 and 64 years use *cannabis* preparations for non-medical purposes (UNODOC 2016). Estimates suggest that roughly 4 – 8 % of the adult population have been affected at some point in their lives by cannabis-use disorders. A growing demand for related therapies can be seen here (WHO 2016). *Cannabis* preparations are usually smoked for the purpose of getting "high". The doses of Δ^9-THC ingested here can be subject to great fluctuations and cannot be listed precisely. Estimates of the uptake of Δ^9-THC for the purpose of intoxication range from an effective inhalative exposure of only a few milligrams to several hundreds of milligrams per day (WHO 1997).

In addition to the use of hemp-containing foods for their intended purpose, it is the view of the BfR that there is also a possibility that certain hemp products can be misused. While the seeds and the oil made from them do not contain any natural Δ^9-THC, the substance is an ingredient of the leaves and flowers. For this reason, it appears to the BfR that the leaves and flowers are of particular relevance with regard to misuse. The Δ^9-THC level of the industrial hemp varieties used in the food sector in Europe may also amount to up to 0.2 % (w/w) in relation to the dry mass. Theoretically, therefore, up to 200 mg Δ^9-THC could be extracted from 100 g of hemp leaves under the right conditions. The Internet provides tips on how to extract Δ^9-THC from food hemp.

3.2   Quality of the data used

The consequences of the existing data gaps and quality of the data available and used in this opinion are discussed below.

3.2.1   Assessment of the data situation from a toxicological point of view

In connection with the appraisal of the hazard potential of Δ^9-THC, it has to be taken into account that the ARfD for Δ^9-THC of 0.001 mg/kg bw per day derived by EFSA, as well as the intake recommendation of 0.001 - 0.002 mg/kg bw per day derived by the BgVV, are based primarily on studies conducted on sick people (BgVV 1997; EFSA 2015). Sick individuals should be regarded fundamentally as a particularly sensitive group. In the studies conducted on healthy respondents, which were also considered by EFSA, (EFSA 2015), the

survey participants had already consumed *cannabis* at some time in the past before participating in the study, so they could possibly have reacted less sensitively due to habituation effects.

Pharmacological effects of other cannabinoids contained in the hemp plant are described in the literature (EFSA 2015; Izzo *et al.* 2009). At the moment, however, the data situation does not allow any final assessment of the resultant risk.

Substance interactions which could influence the effect of Δ^9-THC are also conceivable. On the basis of the available data, it has not been possible up to now to make a conclusive statement on the possible interactions of the more than 120 cannabinoids among one another and with other substances, such as medications and food ingredients. The clinical significance of the interactions already known has not been clarified conclusively either (EFSA 2015). The following aspects are of relevance in this specific context:

- Although individual instances of interactions between Δ^9-THC and other cannabinoids contained in the hemp plant have been described in the literature in the past, the clinical relevance of this cannot be evaluated conclusively. Many of the observations published to date appear to be contradictory in parts (EFSA 2015).

- Alcoholic beverages can intensify the effects of Δ^9-THC (Ballard and de Wit 2011; Chesher *et al.* 1976; Lukas and Orozco 2001).

- On the basis of theoretical deliberations, interactions with several other foods appear to be possible. The clinical relevance cannot be reliably estimated in each instance, however, due to the many different combination possibilities and intake quantities. As the systemically available Δ^9-THC is metabolised via enzymes of the cytochrome P450 system (CYP), substances which modulate the activity of CYP enzymes can have an influence on the plasma level of Δ^9-THC. Compounds of this kind are also to be found in food (e.g. CYP inhibition through ingredients contained in grapefruit or CYP induction through ingredients of St. John's wort (Aktories *et al.* 2009)), in hemp (CYP inhibition through various cannabinoids (Stout and Cimino 2014)) or in medications (CYP inhibition or induction; (Aktories *et al.* 2009)).

- There are known interactions between Δ^9-THC and medications. Anti-depressants, for example, as well as sedatives and antihistamines, can enhance the effects of Δ^9-THC (FDA 2004). The clinical relevance cannot be reliably estimated in each instance, however, due to the many different combination possibilities and intake quantities.

3.2.2   Assessment of the quality of data from a chemical-analytical point of view

A number of methodological limitations mean that it is not possible to exactly determine the actual levels of Δ^9-THC in various foods. The following aspects can influence the results of analysis and are discussed in more detail below:

- Limitations related to the use of the official testing method ASU L 47.00-9:2004-12

- Carryover of Δ^9-THC and Δ^9-THCA-A from the dry material into the aqueous infusion

- Influence of decarboxylation of Δ^9-THCA-A to Δ^9-THC during processing of the food in question

Taking all relevant aspects into consideration, the BfR comes to the conclusion that the method proposed by the regional state authority leads to results that make adequate allowance for the existing uncertainties.

Assessment of the official test method ASU L 47.00-9:2004-12

The regional state authority proposes determining the Δ^9-THC level of hemp-containing tea-like products in dry material using the official test method ASU L 47.00-9:2004-12: After extraction of a 1 g finely ground homogenised sample from the dry product with methanol, Δ^9-THC is detected by means of gas chromatography–mass spectrometry (GC-MS). In addition to Δ^9-THC, Δ^9-THCA-A is simultanously extracted with methanol. The high temperatures in the GC injector (250 °C) catalyse decarboxylation of Δ^9-THCA-A to Δ^9-THC. For this reason, this method determines the sum of psychoactive Δ^9-THC and non-psychoactive Δ^9-THCA-A as total Δ^9-THC. The method was checked in a round robin test with eight participating laboratories (Heinke *et al.* 2002).

From an analytical perspective, the decarboxylation of Δ^9-THCA-A to Δ^9-THC could result in over-determination of Δ^9-THC. Incomplete conversion of Δ^9-THCA-A to Δ^9-THC in the GC injector would result in an under-determination of the total Δ^9-THC level. The maximum conversion rate of Δ^9-THCA-A to Δ^9-THC in the GC oven and in the GC injector is about 70% (Dussy *et al.* 2005) because Δ^9-THC is also subject to thermal degradation from a temperature of 160 °C (Figure 8).
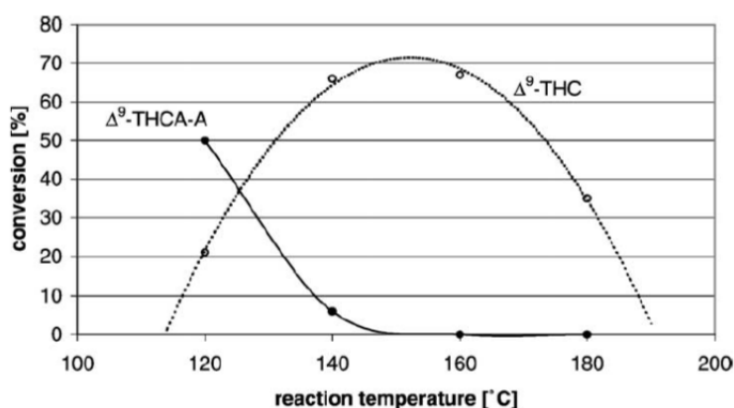
Figure 8: Conversion of Δ^9-THCA-A to Δ^9-THC at different temperatures in the GC oven. Source: Dussy *et al.* 2005.

From an analytical perspective, Δ^9-THC and Δ^9-THCA-A can be measured individually by means of high-performance liquid chromatography (HPLC)-MS/MS (Aizpurua-Olaizola *et al.* 2014). Supercritical fluid chromatography (SFC) with photodiode array detection – with or without connection to a mass spectrometer – also represents a suitable method for individually determining acidic and neutral cannabinoids (Wang *et al.* 2017). For the extraction of Δ^9-THC and other cannabinoids from 100 mg ground dry mass, the extraction efficiency with SFC (CO_2 and 20% ethanol as cosolvent) was greater than 90% (Omar *et al.* 2013). These methods have not yet been validated in a round robin test and their suitability as official analysis methods for different foods still needs to be examined. Other cannabinoids in hemp samples could also be measured with this method.

Carryover of Δ^9-THC and Δ^9-THCA-A from the dry material into the aqueous infusion

The Dutch Office of Medicinal Cannabis (OMC) advises consumers to prepare hemp tea for medicinal purposes according to the following standard procedure: "1 g medicinal hemp is placed in 1 litre of boiling water and boiled for 15 minutes. Particles are filtered out using a tea strainer. The tea can then be consumed immediately or stored in a closed bottle with one spoon of coffee whitener in the fridge for up to five days" (Hazekamp *et al.* 2007; OMC 2017). With respect to medicinal hemp, this type of preparation is referred to as "standard tea" (Hazekamp *et al.* 2007).

With respect to the carryover of Δ^9-THC into the aqueous solution, the solubility of Δ^9-THC in water (2.8 mg/l at 23 °C) could represent a limiting factor from an analytical perspective. Hazekamp et al. examined the extent to which the amount of cannabis, the boiling time, the storage and the use of solubilising agents influence the Δ^9-THC level in the ready-to-drink infusion of "standard tea". The dry product used for the study had a Δ^9-THCA-A level of 191 mg/g and a Δ^9-THC level of 6 mg/g. The method for the extraction and the validated HPLC method used for the quantification have been published (Hazekamp *et al.* 2004; Hazekamp *et al.* 2007). On average (out of six infusions), one litre infusion of 1 g standard tea contained 10 mg Δ^9-THC and 43 mg Δ^9-THCA-A per litre with variation coefficient of 15 % or 12 %. This Δ^9-THC level, which was subject to relatively low fluctuation, was probably the result of saturation of the aqueous phase with Δ^9-THC in combination with a moderate conversion of Δ^9-THCA-A into Δ^9-THC.

The use of a larger amount (1.5 g) of the dry product for preparation of 1 litre of hemp tea did not result in an increase of the Δ^9-THC and Δ^9-THCA-A level (limited solubility). When the amount of hemp was halved (0.5 g), the Δ^9-THC and Δ^9-THCA-A levels in the infusion were also halved. Increasing the boiling time to 30 minutes resulted in higher Δ^9-THC levels, while the Δ^9-THCA-A levels remained constant. When the infusions are stored in a cool place (+4 to +7 °C), the Δ^9-THC level in the aqueous phase decreases significantly. The addition of coffee whitener as solubilising agent prevented this reduction in contained levels.

Based on these results, recovery tests with standards of Δ^9-THC and Δ^9-THCA-A were conducted. The standards (10 mg Δ^9-THC/l; 43 mg Δ^9-THCA-A/l) were spiked in 1 litre boiling water. Recovery of Δ^9-THC spiked in boiling water was 17 %, and recovery of Δ^9-THCA-A was 63 %. 6.6 % of the originally spiked Δ^9-THCA-A was recovered as Δ^9-THC in the aqueous phase. The remaining proportion of Δ^9-THC and Δ^9-THCA-A was detected as a residue that formed after the 15-minute boiling process. It was therefore concluded that a saturated Δ^9-THC solution had formed and that the conversion of Δ^9-THCA-A to Δ^9-THC is limited by the decarboxylation reaction in boiling water. The results of the spiking experiments provided detailed insights into the chemical behaviour of Δ^9-THC and Δ^9-THCA-A during the tea preparation process. In relative terms, more Δ^9-THCA-A than Δ^9-THC was dissolved in boiling water, which can probably be explained by the higher solubility in water of Δ^9-THCA-A (deprotonated state) as compared to Δ^9-THC. Based on the dose level of 10 mg Δ^9-THC/l, 1.7 mg Δ^9-THC/l (17 %) was recovered. This value is only slightly lower than the maximum solubility of Δ^9-THC in water (2.8 mg/l).

Lachenmeier et al. (2004) studied hemp tea and hemp tea with fruits, lemon balm or lemon with respect to their Δ^9-THC level in the dry product and in the infusion. For the tea infusion, 1.5 g of the tea-like product was added to 100 ml boiling water and filtered after an infusion

time of 15 minutes. To extract the cannabinoids from the dry product and the tea infusion, *headspace solid-phase microextraction* (HS-SPME), on the one hand, and a liquid-liquid extraction with n-hexane ethyl acetate, on the other hand, were used. After extraction of the analytes, derivatisation with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (silylation) takes place for the analysis with GC-MS. It is not described whether this derivatisation is suitable for preventing decarboxylation of the extracted Δ^9-THCA-A in the GC injector. The given levels of Δ^9-THC and Δ^9-THCA-A were specified in mg/kg for both the tea leaves and the infusion. This gives rise to the question of whether the specified level also applies to the infusion solution (mg/l). Under the assumption that the levels relate to one litre of the infusion, the carryover of Δ^9-THC from 1.5 g dry product to 100 ml tea infusion was derived (Table 1). Carryover of Δ^9-THC from pure cannabis herb is 99 % for the HS-SPME and 135 % for liquid-liquid extraction. Under the assumption that derivatised Δ^9-THCA-A could be converted to derivatised Δ^9-THC, the data from Lachenmeier et al. (2004) do not provide evidence that fruit components promote the carryover of Δ^9-THCA-A into the infusion solution. The carryover of Δ^9-THC into the infusion solution was lower in tea-like products with lemon (42 %; 32 %), fruits (47 %, 85 %) or lemon balm (32 %; 18 %) than the carryover of Δ^9-THC from pure cannabis herb.

In the context of the method validation study on ASU L 47.00-9:2004-12, significant fluctuations were observed in terms of the carryover of total Δ^9-THC from the dry material into the aqueous solution (Heinke *et al.* 2002). The scatter of the measured values was so great that the method for infusions was not included in the collection of methods. The inhomogeneity of the sample material and differences in the sample matrices could be reasons for this. From an analytical perspective, detailed investigations including the factors inhomogeneity, sample matrix and extraction must first be planned in order to clarify whether hydrochloric extraction has a significant effect on the extraction efficiency of Δ^9-THCA-A.

Table 1: Level of Δ^9-THC in the dry product (DP) as well as in the infusion, and the carryover of Δ^9-THC from the DP into the infusion calculated from this (1.5 g tea in 100 ml water). The levels were determined using GC-MS. According to Lachenmeier *et al.* 2004.

Hemp-containing tea-like product	Extraction	Δ^9-THC				
		mg/kg DP	Infusion*	mg/1.5 g DP	mg/100 ml Infusion	Transfer in % DP → Infusion
Tea with fruits	SPME	4.37	0.05	0.0066	0.0050	76
	LLE	5.19	0.07	0.0078	0.0070	90
Tea (100% hemp leaves)	**SPME**	**15.53**	**0.23**	**0.0233**	**0.0230**	**99**
	LLE	**19.72**	**0.40**	**0.0296**	**0.0400**	**135**
Tea with fruits	SPME	5.73	0.04	0.0086	0.0040	47
	LLE	6.28	0.08	0.0094	0.0080	85
Tea with lemon balm	SPME	8.36	0.04	0.0125	0.0040	32
	LLE	11.11	0.03	0.0167	0.0030	18
Tea with lemon	**SPME**	**14.27**	**0.09**	**0.0214**	**0.0090**	**42**
	LLE	**14.38**	**0.07**	**0.0216**	**0.0070**	**32**

* Figure refers to infusion solution (1 litre ≙ 1 kg).

Effect of decarboxylation of Δ^9-THCA-A to Δ^9-THC during processing

Wang et al. (2016) studied the decarboxylation of Δ^9-THCA-A into Δ^9-THC depending on the temperature with extracts from flowering buds of *Cannabis sativa* L. When dry extracts from *Cannabis sativa* L. are heated, the conversion of Δ^9-THCA-A to Δ^9-THC increases significantly with rising temperatures (e.g. 110 °C) and longer incubation periods. At a temperature of 85 °C, which is to be expected when preparing an infusion in a cup, the decarboxylation of Δ^9-THCA-A is not complete even after 60-minute incubation. The extent to which these studies can be applied to the infusion or other foods is not known.

Conclusion on analysis of Δ^9-THC in foods

Overall, the method of preparing the infusion from hemp-containing tea-like products has a considerable effect on the level of Δ^9-THC from an analytical perspective. The sample amount used, the boiling or infusion time and the time at which preparation of the infusion is begun (cooling to room temperature, preparation of hot infusion, etc.) are significant. To date, there is no official method describing the preparation of standardised tea infusions. The lack of a well-described standardised method for preparing the infusion also makes it difficult to establish a standardised method of analysis.

From an analytical perspective, further studies must be carried out on the inhomogeneity of samples, sample matrix and extraction.

Due to the lack of other validated methods, ASU L 47.00-9:2004-12 can be used for the time being to determine the total Δ^9-THC level in hemp-containing tea-like products, even though this may entail an underestimation of the total Δ^9-THC level. It must be emphasised here that this method measures total Δ^9-THC. For this reason, the data on content levels should also be designated with this nomenclature, and a shortened/simplified designation as Δ^9-THC should be strictly avoided. This method is not suitable if Δ^9-THC and Δ^9-THCA-A need to be measured separately. In such cases, other methods can be used, e.g. LC-MS/MS methods. However, these methods have not yet been validated in a round robin test.

With respect to determining the Δ^9-THC and Δ^9-THCA-A level in infusions, both the homogeneity of the sample matrix and the preparation of the infusion need to be taken into consideration. The method with which the infusion should be analysed then depends on the requirements (determination of total Δ^9-THC level or separate analysis of Δ^9-THC and Δ^9-THCA-A).

Due to the existing analytical uncertainties, it is currently justified in the BfR's opinion to determine the total Δ^9-THC in dry material using the ASU L 47.00-9:2004-12 method. For the subsequent evaluation of the ready-to-drink infusion, a 100 % carryover of total Δ^9-THC should be used as a basis because experimental data indicate significant fluctuations with respect to carryover, so this is currently the only way to achieve a suitable evaluation basis with respect to possible health risks.

3.2.3   Evaluation of the quality of the data used for the exposure estimate

Hemp-containing foods are seldomly consumed foods which are not recorded in the existing consumption data for children and adults. Due to the lack of consumption data, conducting a classical exposure assessment was not possible. To be able to nevertheless evaluate exposure to Δ^9-THC, a method was selected in which – based on BgVV guidance values and

measured content data – theoretical consumption levels were determined which would correspond to an intake level equal to the ARfD. These theoretical consumption levels were compared with the available real data on the consumption levels of analogous foods. This model approach is based on the assumption that the consumption of hemp-containing and analogous foods in relation to one day is similar. These assumptions could either overestimate or underestimate the actual consumption levels.

Furthermore, only a small amount of content data on Δ^9-THC is available for a comprehensive exposure estimate. As already outlined, determination of Δ^9-THC levels is subject to numerous uncertainties with the methods currently used. Moreover, the informative value of data on levels contained could be limited due to the use of different analysis methods for determining these levels. In particular, it is problematic that some methods determine the total Δ^9-THC level as a sum of Δ^9-THCA-A and Δ^9-THC, while other methods selectively measure only Δ^9-THC. It is also possible that total Δ^9-THC levels are sometimes falsely declared as Δ^9-THC for reasons of "simplification".

It should also be pointed out that a complete carryover of total Δ^9-THC from the analysed dry mass of hemp-containing tea-like products to the ready-to-drink infusion was assumed due to the aspects discussed in section 3.2.2.

4   Framework for actions/recommended measures

- *Review of determination methods*

    At present, different methods are used for determining the (total) Δ^9-THC level in foods. A further method for determining levels in plant material exists in the context of the implementation regulation (EU) No. 809/2014 for monitoring the Δ^9-THC levels of hemp types. This method measures total Δ^9-THC. However, according to the regulation, the level is falsely denoted as Δ^9-THC. Determining levels is subject to numerous uncertainties with all methods. To determine (total) Δ^9-THC levels in foods and, ideally, to also monitor levels of hemp types, the BfR recommends establishing standardised methods and a harmonised procedure in the relevant regulation areas in order to guarantee a comparable basis of data. The measured analyte should be clearly declared as total Δ^9-THC or Δ^9-THC. A shortened designation as Δ^9-THC when total Δ^9-THC is meant should be strictly avoided.

    As described in detail, the BfR recommends further studies on the inhomogeneity of samples, sample matrix and extraction. Standardisation of the preparation of infusions of hemp-containing tea-like products is necessary in order to investigate the carryover of Δ^9-THC and Δ^9-THCA-A from the dry product into the infusion solution and for comparability of the results obtained from this. Furthermore, sample preparation for the respective hemp-containing food groups should be optimised, and a measuring method which selectively measures Δ^9-THC and Δ^9-THCA-A should be chosen for validation of the analysis method.

    In this context, there is a need for discussion, for example in the "Working group of food chemistry experts from the federal states and the Federal Office of Consumer Protection and Food Safety (ALS)".

The BfR also sees a need for research with respect to quantitative estimates of the conversion of Δ^9-THCA-A into Δ^9-THC during food processing.

A research project recently initiated at the BfR is intended to study the carryover of Δ^9-THC and Δ^9-THC congeners from hemp-containing feed into cow's milk. An analysis method that enables separate measurement of Δ^9-THC, Δ^9-THCA-A and other Δ^9-THC congeners in different matrices has already been developed in the context of this project together with the Chemical and Veterinary Investigation Office Münsterland-Emscher-Lippe (CVUA-MEL).

- *Improvement of data for estimating exposure*

  Hemp-containing foods are seldomly consumed foods which are not recorded in the existing consumption data for children and adults. The collection of representative data on hemp-containing foods in circulation in Germany and of consumption data on these foods is recommended. Moreover, the collection of reliable content data for different foods with a suitable determination method is recommended, taking account of the aspects outlined above.

- *Further recommendations for action*

  To prevent the guideline values in the relevant hemp-containing foods or the AfRD from being exceeded, the BfR recommends reducing the levels of total Δ^9-THC in foods.

  In the opinion of the BfR, it is possible using suitable procedural measures to reduce the levels in seeds of hemp plants and in foods produced from these seeds. In contrast, hemp-containing tea-like products generally consist of hemp leaves and, in some cases, hemp flowers which can contain Δ^9-THC in relevant amounts. From the perspective of the BfR, it is doubtful whether the levels in these foods can be reliably reduced in order to prevent the guideline values or the AfRD from being exceeded. In addition to the proper use of hemp-containing foods, the BfR also recommends taking the possibility of improper use of certain hemp products into consideration. In this context, the BfR assumes that hemp leaves and flowers appear as being of particular relevance with respect to a potential misuse .

  Through the consumption of certain hemp-containing foods, it is possible that Δ^9-THC doses could be ingested which lie within the range of the doses of ≥ 2.5 milligrams (mg) per person and day used in pharmaceutical products.,In that case pharmacological effects would be expected. The BfR therefore recommends examining whether hemp-containing products with Δ^9-THC levels that may result in intakes in the range of the doses used in pharmaceutical products can still be regarded as foods.

Additional information on the BfR website on the topic of THC in hemp-containing foods

https://www.bfr.bund.de/de/presseinformation/2000/07/bgvv_empfiehlt_richtwerte_fuer_thc__tetrahydrocannabinol__in_hanfhaltigen_lebensmitteln-884.html (in German)

https://www.bfr.bund.de/cm/349/thc-in-feeds-made-from-hemp-and-hemp-products.pdf

BfR "Opinions app"

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