Statement by the European Industrial Hemp Association (EIHA) on the study by the European Food Safety Authority (EFSA) on

Scientific Opinion on the safety of hemp (Cannabis genus) for use as animal feed

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1. Background

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety of hemp (cannabis) for use as animal feed.

EFSA suggested to put whole hemp plant-derived feed materials on the list of materials whose placing on the market or use for animal nutritional purposes is restricted or prohibited and to introduce a maximum THC content of 10 mg/kg to hemp seed-derived feed materials.

This suggestion is based on a LOEL (lowest observed effect level) of THC in humans of 0.04 mg THC/kg bw. By applying an uncertainty factor of 100, a PMTDI (provisional maximum tolerable daily intake) of 0.0004 mg/kg body weight (bw) was derived.

2. Summary of the EIHA statement

The European Industrial Hemp Association (EIHA) welcomes the establishment of guidelines for the THC concentration in animal feed by the European Commission.

EIHA would like to comment on the LOEL and the uncertainty factor suggested by EFSA and proposes in contrast to EFSA a LOEL of 0.07 mg THC/kg bw a day and an uncertainty factor of 20. The LOEL is based on two doses of 2.5 mg THC that is 5 mg per day (70 kg body weight), resulting in an acceptable daily intake (ADI) of 0.0035 mg/kg bw for THC. EIHA does not see much scientific basis for a maximum tolerable daily intake to be provisional and derive a PMTDI since the toxicology of THC is very well investigated in humans, compared with other toxins.

Guideline for maximum THC content to hemp feed materials for farm animals like poultry, pigs, cows and fish, used for food production (meat, milk, eggs)

Based on the derived new LOEL and ADI values and following the methodology of EFSA this would lead to a maximum THC content of 100 mg/kg to hemp seed-derived feed materials.

Furthermore we don't see any reason to prohibit whole hemp plant-derived feed materials in general. Because those feed materials can be used in a five to ten times higher share (up to 100%) in animal feed, we propose **a maximum THC content of 10 mg/kg to whole hemp plant-derived feed materials.**

3. Summary of the rationale for the derivation of the acceptable daily intake (ADI) suggested by EIHA

3.1 Summary of the rationale for the LOEL suggested by EIHA

- The lowest single oral THC dose, at which acute adverse effects, i.e. slightly reduced psychomotor performance, is usually in the range of 5-15 mg. In a few cases 2.5 mg THC, which usually is not distinguishable from a placebo, may cause psychotropic or psychomotor effects. Given that THC effects at low doses (5-20 mg/kg) on psyche and psychomotor performance usually do not last longer than 4-6 hours after oral intake (see Figure 1) two doses of 2.5 mg a day may be taken without increasing adverse effects. This results in a LOEL of 0.07 mg a day for a body weight of 70 kg.

- Adverse chronic effects, such as cognitive changes, structural brain changes, mutagenicity, carcinogenicity, significant changes to hormone levels in males and females, congenital effects, and adverse impact on child development were either not found in humans or were found only at doses significantly higher than the equivalent of oral doses of 10 mg/day, in which cases observed effects were moderate.

- As a rule, for most harmful chemicals the severity of a toxic effect is a function of cumulative exposure, i.e. its exposure concentration and its duration time (Gaylor 2000). Thus, the NOEL correspondingly decreases with the duration of exposure. In the case of THC, the opposite applies since the effect of a given exposure level decreases with time. This is due to the development of tolerance to THC at the cannabinoid receptors.

3.2 Summary of the rationale for the uncertainty factor suggested by EIHA

- Large clinical studies have shown that there is considerable interindividual variation in susceptibility to THC and that some adults may experience slight psychotropic or psychomotor effects at twice a dose of 2.5 mg (or 0.07 mg/kg bw), while most individuals show only effects at considerable higher doses. This variation may be based on genetic polymorphisms of the genes encoding the cannabinoid receptors and the enzymes responsible for the metabolism of THC. We suggest an uncertainty factor of 2 since an uncertainty of any origin is already largely taken into consideration by choosing a low LOEL.

- Since THC may easily cross the placenta to the foetus and the foetus may be more susceptible than children and adults we suggest an uncertainty factor of 5 for a possible higher susceptibility of foetuses and neonates with still not fully developed drug metabolizing enzymes. It is known from clinical studies that children tolorate higher doses of THC with regard to body weight compared to adults. In addition toxic effects from cannabis on the foetus, which have been observed in epidimiological studies are relatively low compared to other drugs. Therefore, an uncertainty factor of 5 should offer a sufficient margin of safety.

- Since the effects of THC may be potentiated by ethanol and other drugs in foetuses, newborns and adults we suggest an uncertainty factor of 2 for interactions with other substances. There is no hint for a measurable potentiation of THC effects with an oral dose of 2.5 mg twice daily by alcohol or other drugs. An uncertainty factor of 2 should offer a sufficient margin of safety.

- We do not suggest an additional uncertainty factor for different percentages of adipose tissue in different individuals as ESFA did, since obese subjects are not found among foetuses and newborns, which means that obese individuals are already protected by the uncertainty factor of 5 in this category. An additional uncertainty factor for obese subjects would only alow for additional protection of obese foetuses and newborns. However, the percentage of adipose tissue in foetuses and newborns is limited and compared to adults there is no large interindividual variation.
- These totals to an uncertainty factor of 20.

3.3 ADI suggested by EIHA

- Based on the above, an acceptable daily intake (ADI) for orally ingested THC of 0.0035 mg/kg bw was assumed to provide protection from both acute and chronic adverse effects to humans.

3.4 ADI versus PMTDI

EFSA suggests a provisional maximum tolerable daily intake (PMTDI), which is mainly based on discrepancies between animal studies and observations in humans concerning neuroendocrine effects. EIHA suggests an acceptable daily intake (ADI) since research conducted on neuroendocrine effects in humans do not justify the assumption that potential adverse effects may be underestimated and that the acceptable daily intake should be provisional.

4. Pharmacological and toxicological basis for the ADI as suggested by EIHA

4.1 Pharmacological basis for a LOEL

Several clinical studies have been conducted which allows the determination of a LOEL for THC. Lucas & Laszlo (1980) found pronounced psychotropic reactions (anxiety, marked visual distortions) in patients undergoing cancer chemotherapy that had received oral doses of 15 mg THC/m^2 (square meter of body surface) corresponding to 25 mg THC for an average adult (body surface: 1.7 m^2). A reduction to 5 mg THC/m^2, about 8-10 mg THC, produced only mild reactions. In a study by Frytak et al. (1984), oral administration of 15 mg THC to 38 cancer patients caused psychotropic effects in 58 % while 42 % experienced no effects. Brenneisen et al. (1996) administered single oral doses of 10 or 15 mg THC to two patients. Physiologic parameters (heart rate) and psychological parameters (concentration, mood) were not modified by the administration. The authors suggest a threshold for psychotropic effects of 0.2-0.3 mg/kg bw. In a study with patients suffering from spasticity due to spinal cord injury by Hagenbach et al. (2007) patients tolerated daily doses of 15-60 mg oral THC.

EFSA cited a study by Chesher et al. (1990) of a healthy population dosed orally with 5 mg of THC following a light breakfast. No difference in the subjective level of intoxication was found relative to placebo controls. Doses of 10 and 15 mg THC respectively caused slight differences relative to a placebo. An oral dose of 20 mg caused marked differences in subjective perception. In several clinical studies, psychotropic reactions were also observed following a single dose of 5 mg THC (Petro & Ellenberger 1981). However, these were generally indistinguishable from effects observed after the administration of placebos.

As pointed out by EFSA, at the lowest administered oral dose of 5 mg, Chesher et al. (1990) observed a decrease in several psychomotoric performance scores, primarily related to standing steadiness, reaction time, and arithmetic performance. It should be noted that the observed effects were small. Findings by other researchers suggest that even doses of 10 or 15 mg of orally administered THC generally result in minor psychomotoric effects (Brenneisen et al. 1996). With reference to the study by Chesher et al. (1990), where authors concluded that an effect on skill performances can occur with a single oral dose of 5 mg THC/person, EFSA suggests that this corresponds "to 0.06 mg/kg bw calculated for the highest individual body weight." EIHA suggests that a LOEL for THC should be based on two doses a day, since effects after oral administration usually last about 4-6 hours and the daily dose of THC in food is usually not consumed in one meal.

EFSA also refers to a review by Ramaekers et al. (2004) on isolated cognitive functions and psychomotic skills related to driving performance to indicate that "THC at doses between 0.04 and 0.30 mg/kg bw causes a dose-dependent reduction in performance," as observed in different tests. However, most of these effects have been investigated after inhalation of THC (cannabis) and Ramaekers et al. (2004) stated that the "magnitude of the THC effects on performance furthermore varied with the application form, i.e. smoking or oral intake, and time post THC use." It is well-known that THC effects are

considerably stronger after smoking (inhalation), and that the lowest effect doses have been observed after smoking (see Figure 1). Thus, the review by Ramaekers does not allow to derive a LOEL for THC of 0.04 mg/kg bw for oral intake as suggested by EFSA.

With regard to repeated exposure of THC EFSA refers to two studies by Beal et al. (1995, 1997), in which HIV patients received oral THC. The first study was a placebo controlled study with 139 patients, who received either THC (2 x 2.5 mg/person daily) or placebo for 42 days (Beal et al. 1995). The second study was an open long-term study, where patients received THC for 12 months (Beal et al. 1997). In the first study 25/72 (about 35 %) patients experienced psychotropic effects. In the long-term study similar effects were observed. However, an open clinical study is not very useful to assess psychotropic effects of THC since similar effects may be observed after placebo (see for example the study by Strasser et al. (2006) below).

EFSA states that "fewer reports are available on the effects of a repeated exposure to THC in humans" without citing any clinical study conducted in the past 10 years where several clinical studies, some of them large-scale, with oral THC and oral cannabis extracts with high concentrations of THC have been conducted (e.g. Wade et al. 2004, Strasser et al. 2006, Rog et al. 2005, Zajicek et al. 2003, 2005, Collin et al. 2007, Narang et al. 2008, Novotna et al. 2011). One of these cannabis extracts (Sativex) has recently been approved as a medicinal drug in the UK, Spain, the Czech Republic and Germany.

Strasser et al. (2006) investigated the effects of THC (2.5 mg twice daily) in cancer patients in a placebo controlled three-arm study with THC, a cannabis extract and a placebo. 243 patients were randomly assigned and 164 completed the six-week trial. In contrast to the study by Beal et al. (1995) with HIV patients, who received the same dose for the same period of time, no differences where observed between THC and placebo for THC-related toxicity and other effects. Thus, a THC dose of 2.5 mg twice daily may be usually regarded as a placebo dose with regard to toxic THC effects.

The largest clinical study ever conducted with THC was a 15-week three-arm study on THC, a cannabis extract and placebo in patients with multiple sclerosis (Zajicek et al. 2003). Patients was offered the possibility to continue into a 12-month follow-up study, which was also a double-blind placebo-controlled study (Zajicek et al. 2005). In the short-term study 611 patients and in the long-term study 502 patients were evaluable. In the short-term study doses were slowly increased up to the occurrence of side effects or until the maximum dose (10-25 mg THC/day depending on body weight) was reached. The maximum dose was 10 mg for participants with a body weight below 50 kg and 25 mg for those with a body weight above 89 kg. Mean daily doses after the dose finding phase for participants with a body weight of 50-69 kg was 11.5 mg (or 0.17-0.23 mg/kg bw) and for participants with a body weight of 70-89 kg 15.8 mg (or 0.18-0.23 mg/kg bw). Thus, mean daily tolerable doses were about 0.2 mg THC/kg bw.

Adverse event	Short-term study (15 weeks)			Long-term study (52 weeks)		
	THC	Cannabis	Placebo	THC	Cannabis	Placebo
Dizzy or lightheadedness	59%	50%	18%	8%	10%	2%
Sleep	35%	40%	33%	8%	8%	9%
Spasms or stiffness	34%	33%	33%	14%	15%	14%
Gastrointestinal tract	30%	37%	20%	9%	12%	7%
Miscellaneous	28%	30%	22%	7%	7%	7%
Pain	26%	24%	32%	10%	17%	10%
Dry mouth	26%	20%	7%	2%	1%	1%
Weakness or reduced mobility	25%	23%	20%	10%	12%	16%
Bladder	24%	26%	23%	10%	12%	15%
Infection	15%	16%	17%	9%	11%	11%
Tremor or lack of coordination	12%	10%	8%	5%	2%	2%
Depression or anxiety	10%	9%	8%	6%	6%	5%
Numbness or paraesthesia	9%	7%	7%	5%	4%	4%
Vision	6%	8%	2%	2%	2%	0%
MS-relapse or exacerbation *)	–	–	–	5%	6%	6%
Falls *)	–	–	–	4%	7%	3%
Memory or concentration *)	–	–	–	2%	2%	1%
Other skin problems *)	–	–	-	1%	5%	6%
Pressure sores *)	–	–	-	0%	1%	3%

*) Not measured in the short-term study

Table 1: Side effects in the studies by Zajicek et al. (2003, 2005). Mean daily doses: about 0.2 mg/kg bw (see text for detailed information).

Compared to the short-term study the long-term therapy with THC over a course of 12 months resulted in a dramatic reduction of adverse effects (Table 1). This may be due to the development of tolerance for some symptoms and to the establishment of an individual tolerable dose for every patient. In the short term study doses were slowly increased until side effects appeared or the maximum daily dose was reached. Since several participants experienced side effects before reaching their maximum daily dose side effects were observed frequently. However, they were usually mild or moderate in intensity (Zajicek et al. 2003). In the long-term study by Zajicek et al. (2005) the incidence of side effects was no longer higher in the verum groups (THC and cannabis) compared to the placebo group except for the events "dizzy or lightheadedness" and "falls" (Table 1). In studies with THC taken by patients with HIV, similar observations of a reduction in frequency of side effects were made. While about 25% of patients reported a minor CNS-related adverse drug event during the first 2 weeks, only about 4% reported such an event during each of the following six weeks (Marinol prescribing information 2011).

Conclusion: An acute dose of 2.5 mg THC (corresponding to 0.035 mg/kg bw assuming a body weight of 70 kg) may usually be regarded as a placebo dose, albeit this dose rarely may cause mild psychotropic or psychomotor effects in humans. Usually only single doses of 5-15 mg THC cause mild psychotropic effects. 0.07

- **The effects of a single dose of THC typically last for 4 to 6 hours (see Figure 1). Thus, the ingestion of an oral dose of 2.5 mg of THC twice per day, equivalent to 5 mg taken over the course of a day, represents the LOEL for any psychotropic effects or the reduction in psychomotor performance. EIHA suggests 0.07 mg/kg bw as a reasonable LOEL for THC, which includes any increased susceptibility in certain individuals**

4.2 Pharmacological basis for the uncertainty factor

EFSA argues that four factors should be considered as risk factors in deriving threshhold limits for THC in humans: (1) Increased sensitivity of neonates and infants, (2) genetic polymorphisms, (3) interaction with other drugs, and (4) body mass index.

4.2.1 Increased sensitivity of children, neonates and foetuses

Children are considered particularly sensitive to many harmful chemicals. Consequently, higher safety factors are chosen to provide adequate protection. However, clinical studies have indicated that children are less sensitive to the effects of THC effects (Abrahamov et al. 1995, Dalzell et al. 1986).

One study on cannabinoid receptor density (Glass et al. 1997) found a similar receptor density in the human foetus and children compared to adults. Other researchers have found that cannabinoid receptor density increases fivefold from birth to adulthood in rats (Belue et al. 1995). In another study low numbers of cannabinoid receptors could be observed as early as the 14th week of gestation in humans (Biegon & Kerman 2001). Receptor density increased slowly but did not reach adult levels by the end of the 24th week.

Glass et al. (1997) found that the fetal and neonatal human brains show patterns of receptor distribution similar to those observed in the adult human brain. They found a similar density of CB receptors in several parts of the brain (neocortex, cerebellum) and a greater density in children in other parts (midbrain, basal ganglia). The authors admit some limitations of their study: "Due to the small numbers of cases available for the study, it is not possible to draw any definitive conclusions on the precise levels of cannabinoid receptors
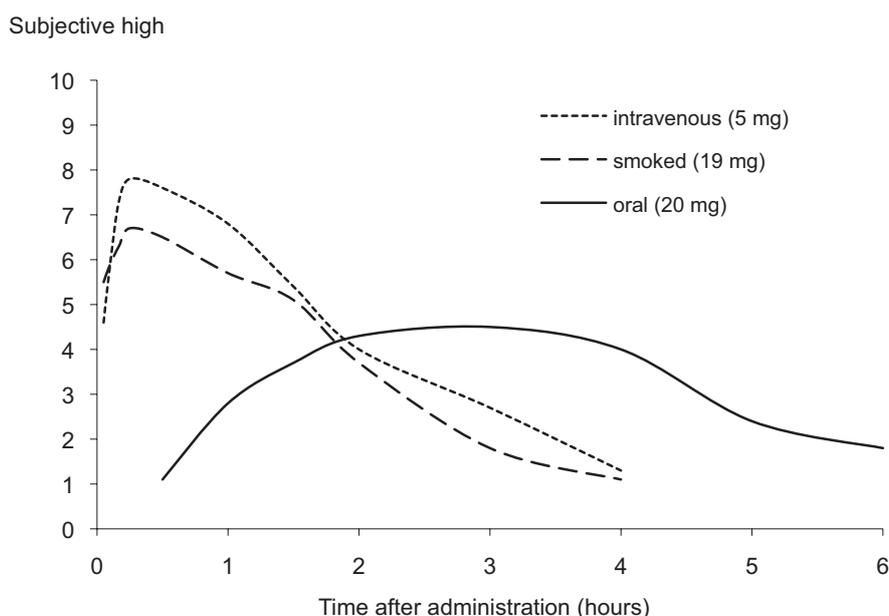

Figure 1: Time course of subjective effects following three modes of administration. A rating of the degree of "high" was made by subjects on a 0 to 10 scale (estimated from figures of Hollister et al. (1981) and Ohlsson et al. (1980)). Taken from Grotenhermen (2003).

binding within the developing brain. Also, since the fetal/neonatal and adult tissue was not processed together, considerable care must be taken in comparing the results of the fetal/neonatal studies with the results in the adult brains" (Glass et al. 1997).

These observations contrast to the results of a study by Belue et al. (1995), who found that cannabinoid receptor density in rats increases fivefold from birth to adulthood. Also, Rodriguez de Fonseca et al. (1993) found an increase in CB binding in rats between birth and day 30, followed by a slight decrease until adulthood (day 60 and later). Another group (McLaughlin et al. 1994) found that cannabinoid receptor mRNA (messenger ribonucleic acid) is present at adult levels as early as postnatal day 3, while CB binding increased almost 50% with increasing age. The last study may resolve some of the contradictions between the different studies since receptor density may be high in infants and children while receptor activity may be low.

In the study by Biegon & Kerman (2001), the pre- and postnatal distribution of human brain CB1 receptors was investigated using quantitative autoradiography with [(3)H]CP55,940 as a ligand. Normal fetal brains (N = 8, gestational age 14-24 weeks) were obtained from voluntary abortions and were compared with normal adult human brains (N = 16, age 18-78). In the fetal human brain, low densities of THC-displaceable, region-specific binding could be observed as early as 14 weeks gestation. Receptor density increased slowly with gestational age but did not reach adult levels by the end of the second trimester (24 weeks gestation). In addition, the distribution pattern in the fetal brains was markedly different from the adult pattern. The most striking difference was the very low density of binding in the fetal caudate and putamen. In contrast, the globus pallidus pars medialis has almost-adult levels of cannabinoid receptors by 17-18 weeks gestation. Authors concluded that "the relatively low and regionally selective appearance of cannabinoid receptors in the fetal human brain may explain the relatively mild and selective nature of postnatal neurobehavioral deficits observed in infants exposed to cannabinoids in utero."

Clinical studies have shown that children tolerate much higher doses of THC than adults before side effects become significant (Abrahamov et al. 1995, Dalzell et al. 1986). In one study, eight children, aged 3 to 10, who underwent chemotherapy, orally received 18 mg delta-8-THC per square meter of body surface, four times daily. Each child received an average of 60 doses, which caused only mild psychotropic side effects in two children and none in the other six. Thus, children with a body surface of 1.0 m^2 received 18 mg THC four times daily. Assuming a body surface of 1.8 m^2 for an adult, this corresponds to single doses of 30 mg and a daily dose of about 120 mg THC. Delta-8-THC is assumed to be somewhat less psychotropic than delta-9-THC, with a relative potency of approximately 75%. Thus, a single 30 mg delta-8-THC dose corresponds to about 23 mg of delta-9-THC, a dose at which adults usually experience considerable psychotropic effects. Authors suggest that the lower CB1 receptor density in children compared to adults may be responsible for the lower susceptability of children to THC.

According to case reports of the Centre for Palliative Medicine and Paediatric Pain Therapy of the University of the Saarland (Germany) THC is an effective and well-tolerated medicinal drug in the treatment of different severe illnesses in children (Gottschling 2011). All children received a slowly increased dose starting with a dose of 0.1 mg/kg bw, which efficiently avoided adverse effects. Mean THC dose was about 0.2 mg/kg bw in children with spasticity and pain after finishing dose finding.

In both humans and animals, transfer of THC to the vascular system of the foetus occurs across the placenta. The time course of THC-concentration in fetal blood is strongly correlated to that in maternal blood, though fetal plasma concentrations were found to be lower compared to the maternal level in rats (Hutchings et al. 1989), in sheep (Abrams et al. 1985–1986), in dogs (Martin et al. 1977), and in monkeys (Bailey et al. 1987).

Following oral intake of THC by the mother, the ratio between fetal and maternal THC levels in plasma appear to be much lower – about one to ten – compared to intravenous and inhalative THC intake, where fetal THC levels are about one third of the mother's. This is likely attributable to the difference in metabolic pathways between oral, inhalative (smoking), and intravenous administration. In a study on dogs, the brain of the fetus showed a THC concentration of one third of the mother's concentration half an hour after intravenous administration (Martin et al. 1977). This relation was also maintained with multiple administrations, indicating that the maternal plasma THC and not the fetal tissue is the actual source for the fetal plasma THC.

The only conclusive study on THC transfer following oral administration was carried out with rats (Hutchings et al. 1989). Two multiple-dose groups were administered either 15 or 50 mg/kg THC once daily during the last two weeks of gestation. Two single dose groups were given the same dose as above but only once on the last day of gestation. Sixty minutes after receiving the last dose, plasma THC levels of all dams and their fetuses were analyzed. Among the dams, plasma concentrations co-varied with dose, and multiple dosing produced higher concentrations than acute dosing, especially at the high dose. Among the fetuses, both in the acute and the chronic dosing group, plasma concentrations were approximately 10% of those found in the dams.

An additional difference between inhalative and oral intake is the much lower maximal peak concentrations of THC following the oral route. Inhalation of a single dose of 10–20 mg THC will result in THC peak plasma concentration in the order of about 50–100 ng/ml, whereas the same oral dose will result in a broader, less pronounced peak with maximum concentrations of typically 5 ng/ml (Grotenhermen 2003). This will also result in a lower broader THC peak in the fetal plasma. Since higher peak concentrations result in stronger effects for the same route of administration, it can be assumed that the fetus is less affected following oral ingestion, since oral and inhalative route of administration of the mother result in the same supply route for the fetus, i.e. the blood vessels of the umbilical cord.

This indicates that the absence of cognitive effects in the children of mothers who used oral cannabis in a Jamaican study (Dreher et al. 1994) may be due in part to the inefficient transfer, thus low fetal toxicity, of THC ingested by pregnant women.

Conclusion: Fetuses experience significant exposure to THC following maternal cannabis ingestion. However, due to different metabolic routes for oral and inhalative THC, fetal exposure after oral THC intake by the mother, e.g., with hemp foods, will be lower compared to inhalative THC intake by the mother, e.g., by smoking

	Inhalation (smoking a cannabis cigarette)	Oral intake (hemp)
Systemic bioavailability	20%	10%
Ratio of ingested THC to THC systemically available	1/5	1/10
Ratio of THC concentration in fetal and maternal plasma	1/3	1/10
Overall ratio	1/15	1/100

Table 2: Comparison of dose-specific fetal toxicity caused by maternal ingestion vs. inhalation of THC.

cannabis cigarettes. Assuming a systemic bioavailability of oral THC of about half that of inhaled THC (10 vs. 20%) and a fetus/mother plasma level ratio of 1:10, compared to 1:3 for inhaled THC, fetal exposure to THC ingested by the mother is about one-sixth of the exposure caused by the inhalation of the same dose (see Table 2). In addition, oral ingestion by the mother results in a much lower maximum peak concentration compared to inhalation of the same dose, further reducing possible impacts from THC. These differences in the transfer to the fetus between oral and inhalative uptake of THC thus provide an additional margin of safety from potential teratogenic effects.

4.2.2 Genetic variation in the genes encoding CB receptors and metabolizing enzymes

There is considerable interindividual variation in the THC doses which result in pharmacological effects. This may be due to variations in polymorphisms of the specific genes (CNR1 and CNR2) that encode the most well-defined cannabinoid receptors (CB1 and CB2) and polymorphisms in the enzymes that are mainly responsible for the degradation of THC in the liver (mainly CYP2C9).

Sachse-Seeboth et al. (2009) investigated the impact of the CYP2C9 polymorphism on the pharmacokinetics of orally administered THC in 43 healthy volunteers. THC pharmacokinetics did not differ by CYP2C9*2 allele status. However, the median area under the curve of THC was threefold higher and that of the metabolite THC-COOH was 70% lower in CYP2C9*3/*3 homozygotes than in CYP2C9*1/*1 homozygotes. CYP2C9*3 carriers also showed a trend toward increased sedation following administration of THC. They concluded that "the CYP2C9*3 variant may influence both the therapeutic and adverse effects of THC." Four of the 43 volunteers were carriers of the CYP2C9*3/*3 variant with a median maximum THC concentration in plasma of 6.3 ng/ml compared to a median of 2.7 ng/ml in carriers of CYP2C9*1/*1. It is reasonable to believe that several patients in the large clinical studies conducted with THC in recent years were carriers of the CYP2C9*3/*3 and this fact might have been the reason that in some studies even doses of 2.5-5 mg twice daily may have caused psychotropic effects since these carriers may have presented with comparably higher THC concentrations in blood at these low doses compared to other patients.

4.3 Pharmacological basis for deriving an ADI and not a PMTDI

EFSA states that "only a very limited number of the experimental studies performed in people" did address neuroendocine effects, which is not quite true, since a large number of studies have been conducted, of which only two are cited in the EFSA review.

EFSA states that "a current risk assessment could only be provisional and based on psychotropic effects observed in humans." It refers to "the lack of conclusive data for neuroendocrine effects in humans" and hinting to a study by Wenger et al. (1988), who found neuroendocrine effects of THC at very low doses of 0.001 mg/kg bw/day administered intraperitoneally to rats, concluding that "the FEEDAP Panel cannot exclude that the provisional risk assessment underestimates potential adverse effects, in particular for foetuses and newborns."

For more than 20 years an epidemiological study is conducted at the University of Pittsburgh, USA, with more than 700 children of mothers who used cannabis and other drugs during pregnancy. These children are examined regularly since their birth and results have been published since then in more than 20 papers (e.g. Scher et al. 1988, Gray et al. 2005, Day et al. 2006, Willford et al. 2010, Day et al. 2011). For more than 30 years a somewhat smaller epidemiological study with about 300 children is conducted at Carleton University in Ottawa, Canada, which resulted in an even larger literature on THC effects on foetuses in humans (e.g. Fried 1980, Fried 1995, Smith et al. 2004, Fried et al. 2005). Both longitutinal studies allow a good understanding of the consequences of THC exposure by the inhalation of cannabis to the foetus and the consequences to later life. It is no longer necessary to rely on studies with rats.

In addition, the relevance of animal studies, which found increased risk of stillbirth and other adverse effects on the fetus following peritoneal injection of THC, to humans, is in principal highly questionable. No such effects had been found with humans after oral or inhalative administration of much higher doses. The same applies to the reported impact of low THC doses on hormone levels in pregnant rats. There are several indications that the effects observed by Wenger and his colleagues should not be extrapolated to humans. E.g., in one of their studies (1989), i.p. injection of 0.001 mg/kg THC during the 3rd week of pregnancy in rats caused a significant prolongation of pregnancy and 42% of stillbirths. This contrasts strongly to studies in humans. There are many studies of pregnancy outcome in users of cannabis. None of them reported any increase of stillbirths relative to controls who did not consume cannabis or a prolongation of pregnancy.

Wenger and his colleagues also reported significant alterations following very low doses of intraperitoneally administered THC, including a reduced LH concentration after i.p. injection of 0.001 mg/kg THC over the 1st, 2nd or 3rd week of pregnancy in rats (Wenger et al. 1988). In contrast, Tyrey (1980) administered intravenous THC in doses of 0.0312 to 0.5 mg/kg to female ovariectomized rats and found no effects on LH secretion at the lowest dose of 0.0312 mg/kg

Target effect	Animal study	Human study
Male plasma testosterone hormone concentration	• 0.1 mg/kg oral THC resulted in decrease in male rats (Steger et al. 1991).	• 0.15 mg/kg oral THC three times daily did not cause an effect (Dax et al. 1989). • 0.25 mg/kg inhaled THC three times daily did not cause an effect (Dax et al. 1989).
Male prolactin level in plasma	• Increase following 0.04 mg/kg THC intraperitoneally in rats (Daley et al. 1974). • Decrease after 0.5 mg/kg oral THC in rats (Rodriguez De Fonseca et al. 1992).	• No change following about 0.6 mg/kg inhaled THC (Cone et al. 1986). • Chronic cannabis users do not show any significant alteration in their prolactin levels (Vescovi et al. 1992, Cohen 1976).
Female luteinizing hormone (LH) concentration	• 0.0625 mg/kg intravenous THC caused a profound decrease in rats (Tyrey 1980).	• No change in LH level following about 0.3 mg/kg inhaled THC (Mendelson et al. 1985a). • However, a light significant decrement (p < 0.02) was observed when the cannabis was consumed during the luteal phase. Chronic users present a normal LH-level (Block et al. 1991, Dornbush et al. 1978, Kolodny et al. 1979).
Stillbirths	• 0.001 mg/kg intraperitoneally THC resulted in 42% stillbirths (Wenger et al. 1989).	• No increased rate of stillbirths in any human study of female cannabis users.
Duration of pregnancy	• 0.001 mg/kg intraperitoneally THC resulted in an increase of duration of pregnancy (Wenger et al. 1989).	• Most human studies did not find any effect of cannabis use on duration of pregnancy (e.g., Shiono et al. 1995, Day et al. 1991, Zuckerman et al. 1989. Hatch and Bracken 1986). • Some found a decreased length of gestation or a higher rate of premature births (Sherwood et al. 1999, Fried et al. 1984, Gibson et al. 1983).
Birth weight	• 0.001 mg/kg intraperitoneally THC reduced birth weight in rats (Wenger et al. 1991).	• Chronic cannabis use (about 0.1 to 2.0 mg/kg inhaled THC) did not cause reduced birth weight (Shiono et al. 1995, Dreher et al. 1994, several other studies).

and significant effects at 0.0625 mg/kg and higher. It is unclear why an intravenous dose of 0.0312 mg/kg (corresponding to about 0.3 mg/kg oral THC with regard to bioavailabilty) should cause no effects while a 0.001 mg/kg THC dose should cause effects. Considering this contradiction in findings, EIHA suggests to dismiss the findings by Wenger and his colleagues until confirmed independently. It should be noted that the studies by Wenger et al. have been conducted more than 10-20 years ago and no other research group reproduced their findings during this time period.

Steger et al. (1990) found a significant decrease of plasma-LH and testosterone levels following doses of 0.1, 1.0 and 10 mg/kg THC in male rats. There was no dose-response relationship; all doses were equally effective. However much higher THC doses than 0.1 mg/kg had no effect on testosterone levels in humans. E.g., Dax et al. (1989) investigated the effects on male chronic cannabis users of administering orally three times per day 10 mg of THC or inhaling three times per day 18 mg of THC for three days, following at least two weeks of abstinence. These conditions simulate routine cannabis drug use. The researchers did not find any alterations in the plasma testosterone concentration. Mendelson et al. (1978) could not detect any influence on the testosterone level in 27 cannabis users that had consumed a mean of 54 cannabis cigarettes or 120 cannabis cigarettes over a period of 21 days.

In a National Institute on Drug Abuse (NIDA) Research Monograph, Mendelson et al. (1984) stated with regard to the effect of THC on female hormones: "It is clear from the foregoing that THC consistently produces significant changes in pituitary gonadal hormones, which are essential for normal reproductive function in experimental animal models. The major unanswered question is: what is the relevance of these data for human females? There are often marked species differences even within animal models and the degree to which THC induced disruption of pituitary gonadal hormones in animals can be extrapolated to humans is an empirical question. Despite the predictive values (and relative economy) of studying drug effects in animals, the ultimate significance of these findings can only be determined in human studies" (page 105).

Table 3: Selected discrepancies between animal and human data on THC.

Conclusion: Toxicological data from animal studies can help to elucidate the toxicity of cannabinoids in humans. However, comparison of the data from studies on humans and animals reveals often considerable inconsistencies. These may result from not only interspecies differences, but also different routes of administration. Particularly, the suitability of the intraperitoneal route for extrapolation to oral and inhalative exposure has previously been questioned (Abel 1985). The findings by Wenger and his colleagues, which contradict findings from human studies applying much higher doses and using the more representative oral or inhalative routes, are a case in point. Thus, wherever possible, a quantitative risk assessment should be based on data from human studies. EIHA suggests to dismiss the results by Wenger and colleagues and to rely on extensive available human data.

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