

**Supporting document 2**

Cannabidiol hazard profile – Proposal P1042

Low THC Hemp Seeds as Food

**Executive summary**

Cannabidiol (CBD), which is structurally related to delta 9-tetrahydrocannabinol (THC), is typically present in low THC hemp seed foods at levels in the low mg/kg range. The pharmacological properties of CBD, and its safety profile, have been the subject of extensive research, including studies in humans. In contrast to THC, CBD binds weakly to cannabinoid receptors and does not cause psychoactive effects. Studies in laboratory animals indicate that the oral toxicity of CBD is low.

CBD administered by the oral route has been investigated in clinical trials in healthy subjects and in patients with various medical conditions. CBD has been shown to be well tolerated at doses greater than 1000 mg per day. No reports of adverse effects attributable to oral CBD were located in the published literature. Regarding efficacy in these studies, the lowest oral dose in humans for which potential therapeutic effects have been reported is 120 mg/day.

**Table of Contents**

[**Executive summary** 1](#_Toc456883546)

[1 Introduction 2](#_Toc456883547)

[2 Pharmacology and toxicology of CBD 2](#_Toc456883548)

[3 Conclusions 4](#_Toc456883549)

[4 References 5](#_Toc456883550)

# 1 Introduction

Cannabidiol (CBD), which is structurally related to delta 9-tetrahydrocannabinol (THC), is typically present in low THC hemp seed foods at levels in the low mg/kg range (Leizer et al. 2000; Lachenmeier et al. 2004). This supporting document provides an overview of safety information on CBD derived from studies in laboratory animals administered CBD by various routes (e.g. oral, intraperitoneal, intravenous) and in humans administered CBD orally. CBD has been extensively studied in *in vitro* receptor binding and activation assays (e.g. McPartland et al. 2015). In contrast to THC, CBD exhibits weak binding to cannabinoid receptors and does not cause psychoactive effects.

# 2 Pharmacology and toxicology of CBD

**2.1 Studies in laboratory animals**

Acute and repeat-dose toxicity studies in laboratory animals have shown that the oral toxicity of CBD is low (e.g. Rosenkrantz et al. 1981). More recently, published animal studies on CBD have been primarily concerned with the investigation of potential therapeutic effects, such as those relating to analgesia (Coster et al. 2007; Maione et al. 2007; Ward et al. 2014), anti-depressant (El-Alfy et al. 2010; Zanelati et al. 2010), anti-convulsant (Consroe et al. 1982; Jones et al. 2010, 2012; Mao et al. 2015), anti-emetic (Kwiatkowska et al. 2004; Parker et al. 2004; Rock et al. 2012), anti-inflammatory (Borrelli et al. 2009; Schicho et al. 2012) and anti-cancer (Massi et al. 2013) activities. These studies, while focussing on the potential efficacy of CBD as a therapeutic drug, have consistently shown that CBD has a favourable safety profile.

**2.2 Studies in humans**

CBD administered by the oral route has been investigated in clinical trials in healthy subjects and in patients with various medical conditions (Table 1). CBD has been shown to be well tolerated at doses greater than 1000 mg per day. No reports of adverse effects attributable to oral CBD were located in the published literature. Regarding efficacy in these studies, the lowest oral dose in humans for which potential therapeutic effects have been reported is 120 mg/day (Wade et al. 2003).

**Table 1**: Representative studies in humans administered oral cannabidiol

| **Reference** | **Oral CBD dose levels** | **Study design** | **Findings** |
| --- | --- | --- | --- |
| Consroe et al.  (1979) | 200 mg (single dose) | 10 healthy volunteers were given oral placebo (glucose capsule and orange juice), CBD (200 mg capsule and orange juice), alcohol (1 g/kg in orange juice and glucose capsule), and CBD (200 mg capsule) plus alcohol (1 g/kg in orange juice) in a randomized, double-blind, crossover, study. | CBD did not impair motor and mental performance. Alcohol and alcohol plus CBD produced similar levels of impairment. |
| Cunha et al. (1980) | Study 1:  3 mg/kg bw per day for 30 days.  Study 2:  200–300 mg/day for up to 18 weeks. | Study 1: Double-blind, randomised, placebo controlled study in healthy volunteers (n = 8 per group).  Study 2: Double-blind, randomised, placebo controlled study in epileptic patients (n = 8 per group). | Study 1: There were no CBD-related effects on the parameters investigated (neurological and physical examinations, blood and urine analysis, electrocardiogram and electroencephalogram).  Study 2: CBD reduced the incidence and severity of convulsions with no adverse effects on the safety parameters investigated (as for study 1). |
| Consroe et al.  (1991) | 700 mg/day for 6 weeks | Double-blind, cross-over study with placebo and CBD in 15 patients with Huntington's Disease. | CBD treatment was neither symptomatically effective nor associated with adverse effects. |
| Zuardi et al. (1993) | 300 mg (single dose) | Four groups of 10 healthy subjects received, under a double-blind, randomised design, placebo or one of the following: CBD (300 mg), diazepam (10 mg), or ipsapirone (5 mg). | In a simulated public speaking test, CBD relative to placebo had no effect on anxiety before the test, however CBD was associated with decreased anxiety after the test. |
| Wade et al. (2003) | 120 mg/day for 2 weeks | Double-blind, placebo-controlled study in 20 patients with neurogenic disorders/injury. | CBD was associated with lower ratings of pain and spasticity severity, but had no effect on other parameters investigated (e.g. alertness, appetite, sleep). No adverse effects were attributable to CBD treatment. |
| Crippa et al. (2004) | 400 mg (single dose) | Double-blind, cross-over study with placebo and CBD in 10 healthy males. | CBD was associated with decreased subjective anxiety and increased mental sedation. |
| Zuardi et al. (2006) | 40 mg/day increasing to 1280 mg/day over 30 days | Three patients with treatment-resistant schizophrenia were given placebo for 5 days and from the 6th to 35th day (inclusive) received CBD (initial oral dose of 40 mg increasing to 1280 mg/day by day 35). | No adverse effects were attributable to CBD treatment. Regarding efficacy of CBD in treating schizophrenia, one patient showed mild improvement, but the other two patients showed no improvement. |
| Bhattacharyya et al. (2009) | 600 mg (single dose) | Three groups of five healthy males ingested THC (10 mg), CBD (600 mg), or a placebo in a double-blind, randomized design. | CBD did not affect regional brain activation (evaluated using functional magnetic resonance imaging, fMRI), performance in a verbal learning task, or measures of anxiety, intoxication and sedation. |
| Fusar-Poli et al.  (2009) | 600 mg (single dose) | Three groups of five healthy males ingested THC (10 mg), CBD (600 mg), or a placebo in a double-blind, randomized design. | CBD did not affect heart rate, blood pressure and task performance (e.g. reaction time). CBD was associated with reduced anxiety but did not affect other psychological parameters examined. |
| Zuardi et al. (2009) | 150-400 mg/day for 4 weeks | Six patients with Parkinson’s disease received CBD at a starting dose of 150 mg/day increasing to 400 mg/day over 4 weeks, in addition to their usual therapy. | CBD resulted in improvements in Parkinson's disease symptoms. No CBD-related adverse effects were observed. |
| Zuardi et al. (2010) | 600–1200 mg/day for 24 days | Two patients with bipolar affective disorder received CBD at a starting dose of 600 mg/day increasing to 1200 mg/day over 24 days. | CBD was therapeutically ineffective and was not associated with adverse effects. |
| Bergamaschi et al. (2011) | 600 mg (single dose) | 24 patients with social anxiety disorder received either CBD (600 mg; n = 12) or placebo (n = 12) in a double-blind randomized study. Treatment occurred 1.5 hours prior to a simulated public speaking test. | Treatment with CBD reduced anxiety and cognitive impairment during the test. No adverse effects were attributable to CBD. |
| Martin-Santos et al. (2012) | 600 mg (single dose) | A randomised, double-blind, cross-over, placebo controlled trial was conducted in 16 healthy male subjects receiving THC (10 mg), CBD (600 mg), or placebo. | There were no differences between CBD and placebo on psychological and physiological parameters investigated. |
| Englund et al. (2013) | 600 mg (single dose) | Healthy participants were randomised to receive CBD (600 mg; n = 22) or placebo (n = 26), 210 min prior to intravenous (IV) THC (1.5 mg). | Post-THC psychoses/paranoia was less frequent in the CBD group compared with the placebo group. No adverse effects were attributable to CBD. |
| Chagas et al. (2014) | 75 or 300 mg/day for 4 weeks | Double-blind, placebo-controlled, randomised study in 21 patients with Parkinson’s disease. Participants were assigned to three groups of seven subjects each treated with placebo, CBD (75 mg/day) or CBD (300 mg/day) for 4 weeks. | Compared to placebo, the 300 mg/day CBD group scored higher in a quality of life assessment. No adverse effects were attributable to CBD at either dose level. |
| Manini et al. (2015) | 400 or 800 mg (single dose) | Double-blind, placebo-controlled cross-over study in 17 healthy volunteers administered intravenous fentanyl with co-administered CBD (400 or 800 mg) or placebo. | CBD did not exacerbate the adverse effects associated with intravenous fentanyl administration. |

# 3 Conclusions

Clinical studies in humans consistently show that orally administered CBD is well tolerated at doses exceeding 1000 mg/day. No reports of adverse effects attributable to oral CBD were located in the published literature. Regarding efficacy in human studies, the lowest oral dose for which potential therapeutic effects have been reported is 120 mg/day.

# 4 References

Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, Quevedo J, Roesler R, Schröder N, Nardi AE, Martín-Santos R, Hallak JE, Zuardi AW, Crippa JA (2011) Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. Neuropsychopharmacology, 36(6):1219–26.

Bhattacharyya S, Fusar-Poli P, Borgwardt S, Martin-Santos R, Nosarti C, O’Carroll C, Allen P, Seal ML, Fletcher PC, Crippa JA, et al. (2009) Modulation of mediotemporal and ventrostriatal function in humans by delta-9-tetrahydrocannabinol: a neural basis for the effects of *Cannabis sativa* on learning and psychosis. Arch Gen Psychiatry, 66:442–51.

Borrelli F, Aviello G, Romano B, Orlando P, Capasso R, Maiello F, Guadagno F, Petrosino S, Capasso F, Di Marzo V, Izzo AA (2009) Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant *Cannabis sativa*, is protective in a murine model of colitis. J Mol Med (Berl). 87(11):1111–21.

Chagas MH, Zuardi AW, Tumas V, Pena-Pereira MA, Sobreira ET, Bergamaschi MM, dos Santos AC, Teixeira AL, Hallak JE, Crippa JA (2014) Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. J Psychopharmacol. 28(11):1088–98.

Consroe P, Carlini EA, Zwicker AP, Lacerda LA (1979) Interaction of cannabidiol and alcohol in humans. Psychopharmacology (Berl). 66(1):45–50.

Consroe P, Benedito MA, Leite JR, Carlini EA, Mechoulam R (1982) Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice. Eur J Pharmacol. 83:293–8.

Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, Kennedy K, Schram K (1991) Controlled clinical trial of cannabidiol in Huntington’s disease. Pharmacol Biochem Behav, 40:701–8.

Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M (2007) The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. Eur J Pharmacol. 556(1-3):75–83.

Crippa JA, Zuardi AW, Garrido GE, Wichert-Ana L, Guarnieri R, Ferrari L, Azevedo-Marques PM, Hallak JE, McGuire PK, Filho Busatto G (2004) Effects of cannabidiol (CBD) on regional cerebral blood flow. Neuropsychopharmacology, 29(2):417–26.

Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, Sanvito WL, Lander N, Mechoulam R (1980) Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology, 21(3):175–85.

El-Alfy AT, Ivey K, Robinson K, Ahmed S, Radwan M, Slade D, Khan I, ElSohly M, Ross S (2010) Antidepressant-like effect of delta9-tetrahydrocannabinol and other cannabinoids isolated from *Cannabis sativa* L. Pharmacol Biochem Behav. 95(4):434–42.

Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S, Stone JM, Reichenberg A, Brenneisen R, Holt D, Feilding A, Walker L, Murray RM, Kapur S. Cannabidiol inhibits THC-eli paranoid symptoms and hippocampal-dependent memory impairment (2013) J Psychopharmacol. 27(1):19–27.

Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, Seal M, Surguladze SA, O'Carrol C, Atakan Z, Zuardi AW, McGuire PK (2009) Distinct effects of {delta}9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch Gen Psychiatry, 66(1):95–105.

Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, Whalley BJ, Stephens GJ (2010) Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. J Pharmacol Exp Ther. 332:569–77.

Jones NA, Glyn SE, Akiyama S, Hill TD, Hill AJ, Weston SE, Burnett MD, Yamasaki Y, Stephens GJ, Whalley BJ, Williams CM (2012) Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. Seizure, 21:344–52.

Kwiatkowska M, Parker LA, Burton P, Mechoulam R (2004) A comparative analysis of the potential of cannabinoids and ondansetron to suppress cisplatin-induced emesis in the *Suncus murinus* (house musk shrew). Psychopharmacology (Berl). 174(2):254–9.

Lachenmeier DW, Kroener L, Musshoff F, Madea B (2004) Determination of cannabinoids in hemp food products by use of headspace solid-phase microextraction and gas chromatography-mass spectrometry. Anal Bioanal Chem. 378(1):183–9.

Leizer C, Ribnicky D, Poulev A, Dushenkov S, Raskin I (2000) The composition of hemp seed oil and its potential as an important source of nutrition. Journal of Nutraceuticals, Functional & Medical Foods, 2(4):35–53.

Manini AF, Yiannoulos G, Bergamaschi MM, Hernandez S, Olmedo R, Barnes AJ, Winkel G, Sinha R, Jutras-Aswad D, Huestis MA, Hurd YL (2015) Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. J Addict Med. 9(3):204–10.

Maione S, Piscitelli F, Gatta L, Vita D, De Petrocellis L, Palazzo E, de Novellis V, Di Marzo V (2011) Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action. Br J Pharmacol. 162(3):584–96.

Mao K, You C, Lei D, Zhang H (2015) High dosage of cannabidiol (CBD) alleviates pentylenetetrazole-induced epilepsy in rats by exerting an anticonvulsive effect. Int J Clin Exp Med. 8(6):8820–7.

Martin-Santos R, Crippa JA, Batalla A, Bhattacharyya S, Atakan Z, Borgwardt S, Allen P, Seal M, Langohr K, Farré M, Zuardi AW, McGuire PK (2012) Acute effects of a single, oral dose of delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. Curr Pharm Design, 18(32):4966–79.

Massi P, Solinas M, Cinquina V, Parolaro D (2013) Cannabidiol as potential anticancer drug. Br J Clin Pharmacol. 75(2):303–12.

McPartland JM, Duncan M, Di Marzo V, Pertwee RG (2015) Are cannabidiol and Δ(9) -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol. 172:737–53.

Rock EM, Bolognini D, Limebeer CL, Cascio MG, Anavi-Goffer S, Fletcher PJ, Mechoulam R, Pertwee RG, Parker LA (2012) Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT(1A) somatodendritic autoreceptors in the dorsal raphe nucleus. Br J Pharmacol. 165:2620–34.

Rosenkrantz H, Fleischman RW, Grant RJ (1981) Toxicity of short-term administration of cannabinoids to rhesus monkeys. Toxicol Appl Pharmacol, 58(1):118–31.

Schicho R, Storr M (2012) Topical and systemic cannabidiol improves trinitrobenzene sulfonic acid colitis in mice. Pharmacology, 89(3-4):149–55.

Wade DT, Robson P, House H, Makela P, Aram J (2003) A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil. 17(1):21–9.

Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SR (2010) Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. Br J Pharmacol. 159(1):122–8.

Zuardi AW, Cosme RA, Graeff FG, Guimarães FS (1993) Effects of ipsapirone and cannabidiol on human experimental anxiety. J Psychopharmacol. 7(1 Suppl):82–8.

Zuardi AW, Hallak JE, Dursun SM, Morais SL, Sanches RF, Musty RE, Crippa JA (2006) Cannabidiol monotherapy for treatment-resistant schizophrenia. J Psychopharmacol. 20(5):683–6.

Zuardi AW, Crippa JA, Hallak JE, Pinto JP, Chagas MH, Rodrigues GG, Dursun SM, Tumas V (2009) Cannabidiol for the treatment of psychosis in Parkinson's disease. J Psychopharmacol. 23(8):979–83.

Zuardi A, Crippa J, Dursun S, Morais S, Vilela J, Sanches R, Hallak J (2010) Cannabidiol was ineffective for manic episode of bipolar affective disorder. J Psychopharmacol. 24(1):135–7.