FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

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.

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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.

Reference	Oral CBD dose levels	Study design	Findings
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.

Reference	Oral CBD dose levels	Study design	Findings
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.

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