Pharmacodynamic and pharmacokinetic factors impacting the *in vivo* pharmacology and toxicology of K2 synthetic marijuana
• Recent normalization of marijuana use is based to some extent on its well-known safety profile and relatively low toxicity risk.

• References to high-efficacy synthetic cannabinoids as “fake marijuana” have hampered efforts to educate the public about potential toxic effects of these substances.
• High degree of structural diversity among compounds.

• Not unusual to find 2 or more compounds in the same sample.

• All compounds typically possess higher affinity for and efficacy at CB1 receptors as compared to $\Delta^9$-THC, and are usually more potent in vivo.
In 1992, John W. Huffman (Clemson U) began synthesizing a series of several hundred compounds for SAR studies designed to tease out physiological function of CBR subtypes.

R – butyl = JWH-073

R – pentyl = JWH-018

Etc.
Synthetics have higher (JWH-018) or comparable (JWH-073) affinity to $\Delta^9$-THC.
Synthetics are full CB1 agonists, while $\Delta^9$-THC is a partial CB1 agonist.
Essentially all preclinical studies with these compounds involve systemic injection, but the preferred route of administration in human users is via smoking.

products were primarily smoked (via pipe, cigarette, blunt, or water pipe/bong), though administration via vaporization, oral ingestion, and rectal ingestion were also reported.
• Formation of Phase I metabolites is probably maximized when drugs are administered orally or via IP injection, and likely minimized when drugs are smoked. ¹

• Thus, systemic injection of SCBs in laboratory animals may overestimate biological effects due to contribution of active hydroxylated metabolites.

• We therefore compared a range of doses of Δ⁹-THC, JWH-018 and JWH-073 in several in vivo assays after IP injection or inhalation of volatilized compound.

• Apparatus for whole-body exposure to volatilized drugs.

• Mice exposed 3 at a time.

• 10 min exposure, with room air added 5 min into exposure for 60 seconds.
Synthetic Cannabinoids

Tail-flick analgesia

Horizontal bar catalepsy

Hypothermia

Locomotor suppression
• Similar hypothermic effects across routes, and same order of potency.

• Hypothermic effects of inhaled CBs were attenuated by rimonabant pretreatment.
• Similar locomotor effects across routes, and same order of potency.

• Locomotor effects of inhaled CBs were attenuated by rimonabant pretreatment.
• Weaker analgesic effects after inhalation, but same order of potency.

• Effects not really big enough to block with rimonabant.
• Cataleptic effects were **not observed** after inhalation.

• Interesting qualitative differences between $\Delta^9$-THC and SCBs...
Leg splay, full-body jerks, and handling-induced convulsions observed with JWH-018, but not with ∆9-THC, were blocked by rimonabant.
• Convulsions do not occur unless animals are disturbed.

• Convulsions are CB1-mediated, and are completely blocked by rimonabant.
Pretreatment with 150 mg/kg of the global P450-enzyme inhibitor 1-aminobenzotriazole (1-ABT) potentiates hypothermic effects of SCBs – consistent with detoxification?
• Profound tolerance develops to the hypothermic effects of JWH-018
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• Tolerance is still evident in mice injected again 14 days after last drug dose.
• Mice made tolerant to THC (30 mg/kg/day x 4 days) show cross-tolerance to synthetics.

• Greater efficacy does not overcome tolerance?
• SCBs induce $\Delta^9$-THC-like effects in mice when administered IP or by inhalation (except for catalepsy.)

• Order of potency remains the same, and effects are blocked by CB1 antagonist rimonabant.

• Dramatic handling-induced convulsant effects with high doses of SCBs after IP injection, but never observed with $\Delta^9$-THC. These effects are CB1-mediated.

• Inhibition of CYP450 enzymes increases effectiveness and duration of action of SCBs, implying that phase I metabolism is involved in detoxification of these compounds.
Tolerance and cross-tolerance among THC and the synthetics suggests that marijuana users and first-time users will differ greatly in sensitivity to SCBs.
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