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Re: Reproductive Toxicity of Cannabis and Cannabis-Related Chemicals:  
Cannabis, Marijuana smoke, Cannabis Extracts, Delta-9-THC

**Summary:**

- Evidence of reproductive harm due to cannabis is inconclusive and clouded by confounding factors such as smoking, concurrent use of tobacco, and other factors.  
- **To date, human epidemiological studies have focused exclusively on smoked marijuana,** for which exposure to smoke and tobacco use, which are known reproductive risks, are confounding factors. There have been no reproductive studies of orally consumed cannabis, cannabis extracts, sprays, vaporizers, or topicals. THC has historically been the dominant cannabinoid in the smoked marijuana used in human studies. However, in recent years, high-cannabidiol (CBD) and other varieties have become available. There have been no human studies of such varieties nor of smoked or inhaled CBD.  
  - **“Cannabis” and “cannabis extracts” are not chemically well-defined.** Aside from THC, many available extracts contain cannabinoids such as CBD, THC-acid (THCA), CBD-acid (CBDA), THCV (tetrahydrocannabavarin), CBN (cannabinol), delta-8 THC, CBG (cannabigerol) etc. Many such extracts contain no or negligible amounts of delta-9-THC. There have been no scientific studies to determine whether such products present any risk of reproductive harm.  
  - **California law already requires maternal use warning labels on all commercial cannabis products:** “Cannabis use while pregnant or
breastfeeding may be harmful” [CA Code of Regulations, Title 17, Sec. 40404]. An additional Prop 65 warning would therefore seem superfluous and confusing to both consumers and the industry.

Studies of smoked marijuana:

- Studies of marijuana smoking by pregnant women have come to conflicting results. Some studies have suggested an association between fetal exposure to marijuana smoke and lower birth weight. However, the difference may be attributable to concomitant smoking and tobacco use, which are known reproductive risk factors. A comprehensive review of the evidence on prenatal, perinatal, and postnatal exposure to cannabis was published by the National Academy of Sciences in 2017. The NAS concluded (1) there is “substantial evidence” of a statistical association between maternal cannabis smoking and lower birth weight in offspring, and (2) “the relationship between cannabis smoking and other pregnancy and childhood outcomes is unclear.” These conclusions pertain specifically to smoked marijuana of the common THC-dominant type, not to high-CBD or exotic strains, nor oral extracts, edibles, sprays, vaporizers, or topicals, which have never been studied. Other recent analyses have questioned the link between cannabis smoking and adverse pregnancy outcomes. Noting that the “association between maternal marijuana use and adverse pregnancy outcomes may be attributable to concomitant tobacco use and other confounding factors,” a meta-analysis of 31 studies by Conner et al. concluded, “Maternal marijuana use during pregnancy is not an independent risk factor for adverse neonatal outcomes after adjusting for confounding factors.” A population-based study by Ko et al. likewise found “prenatal marijuana use was not independently associated with lower average birthweight or gestational age.” In sum, the totality of evidence fails to show that cannabinoids, cannabis, or its extracts are a reproductive hazard except possibly when smoked.

FDA-approved oral cannabis medicines

1. E.g., a 24- study meta-analysis found infants exposed to cannabis in utero had decreased birth weight and were more likely to be placed in neonatal intensive care. Gunn JK, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. BMJ Open. 2016 Apr. doi: 10.1136/bmjopen-2015-009986.
Two cannabinoid-based oral medicines have undergone FDA review and approval for the U.S. pharmaceutical market: Marinol® (dronabinol), consisting of synthetic THC capsules, and Epidiolex®, a natural CBD extract spray.

The patient package insert for Marinol advises: “Marinol may cause fetal harm,” and “Avoid use in pregnant Women.” However, it does not state that adverse reproductive effects have been proven. Instead, it cites three rodent studies finding no teratogenicity in mice at 30 times the recommended daily dosage, or in rats at 5 times the dosage, or at 3 times the dosage in patients with AIDS and cancer. It goes on to cite studies of human marijuana users that showed reduced birth weight, but which examined only use by smoking, not oral use or vaporization.

Also on the market is Epidiolex®, an oral extract of naturally derived CBD that is FDA approved for the treatment of Lennox-Gastaut and Dravet syndrome. According to its package insert, “There are no adequate data on the developmental risks associated with the use of Epidiolex in pregnant women.” The insert cites three rodent studies. Two of them found no adverse fetal effects at dosages equal to 14 or 9 times the recommended human dose of 20 mg/kg/day. The third found decreased fetal weight and structural variations only at the highest dose tested, which was 125 mg/kg/day. This is extraordinarily high by human standards. The recommended human dosage of Epidiolex is already much higher than what is usually available from cannabis extracts now on the market for other medical conditions. For a 50-kg subject, a standard Epidiolex dose works out to 1,000 mg per day. To reach the level where fetal abnormalities were detectable would require 6,250 mg/day. CBD extracts now on the market commonly range around 2.5 – 30 mg CBD per dose.

In sum, studies of oral cannabis medicines have failed to find appreciable reproductive risks.

Conclusions

In conclusion, there exists no scientific proof that cannabis, cannabis extracts, or delta-9 THC taken orally present a known, meaningful risk of reproductive harm. What does exist is evidence linking maternal marijuana smoking to a higher risk of low birth weight babies. It’s possible this risk has nothing to do with cannabinoids themselves, but rather with smoking, which is a known reproductive risk factor. Marijuana smoke is already on OEHHA’s list of carcinogens. There accordingly exist valid reasons to advise pregnant women to avoid smoking of marijuana.

In fact, however, California cannabis regulations already require warnings against maternal use on all cannabis products. Further OEHHA warnings at this point would therefore seem superfluous and likely only to confuse matters. In the future, health warnings about cannabis would best be coordinated with the
Department of Public Health and Bureau of Cannabis Control, who oversee cannabis regulations. The cannabis industry already has enough to worry about without more superfluous regulations, while California consumers are already bombarded with so many vague and unfocused Prop 65 warnings that they tend to tune out and ignore them.

Sincerely,

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