Alex Azar
Secretary of Health and Human Services
US Department of Health and Human Services
200 Independence Avenue SW
Washington D.C, 20201

November 5, 2019

Dear Secretary Azar:

This letter is to bring to your attention a study underway at the University of Washington referred to as the "Moms and Marijuana Study" and granted under the title: "Olfactory Activation and Brain Development in Infants with Prenatal Cannabis Exposure." The Office of Human Research Protections issued a decision against opening a case on this research, and we are asking you, as the Secretary of Health and Human Services, to overturn that decision based on the scientific concerns we outline in this letter.

Women who are in their first trimester of a pregnancy, who are frequent users of marijuana for morning sickness, are being recruited. The study seeks to assess the damage marijuana prenatal exposure may have on the babies by means of various testing, including an MRI scan of the infants at six months of age. The recruited women will receive $300.00 + for their participation. The study is solely funded by NIDA. This study calls into question serious issues over human rights and raises ethical questions, including mandatory reporting pertaining to substance abuse in pregnancy. This open letter seeks to gather support from you in seeing that this study is re-evaluated at the federal level. The study's website is at the following link: https://depts.washington.edu/klab/infoMM.html

We are of the view that the Kleinhans study does not meet the requirements set forth by the Office of Human Research Protection (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/): "Subpart B presumption that pregnant women may be included in research, provided certain conditions are met. According to Subpart B, the permissibility of research with pregnant women hinges on a judgment of the potential benefits and risks of the research. Approval of proposed research carrying no "prospect of direct benefit" to the woman or fetus requires that the risk to the fetus be judged "not greater than minimal". Fetal risk that exceeds that standard is permissible only when the proposed research offers a prospect of direct benefit to the pregnant woman, the fetus, or both. **Notably, if the proposed research does not fit within either of those two parameters, Subpart B offers an additional mechanism at the national level for approval by the Secretary of Health and Human Services."**

The federal definition of minimum risk reads: *"That the magnitude and probability of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."* Although the primary harm at issue is exposure to marijuana, the use of MRI or *f*MRI has not yet been proven safe for otherwise healthy infants, where an unknown risk would come with no benefit, as there is no diagnosis being sought. The UW study consent form reads on page 3:*"There are no known side effects associated with MRI or fMRI when earphones are used to protect your hearing." …. There may be risks*

associated with the use of magnetic resonance which are not known at this time." It is precisely questions about the potential for MRI risks that should be investigated in an animal model first.

In principle, any study that tracks the consequences of administering a drug to a developing fetus should be carried out in animal models first, and not in humans until the animal results point towards safety. The evidence of decades of research on marijuana in pregnancy does not point to safety but rather to risk and harm.

Two basic principles in bioethics are relied upon to determine the merit of research that involves human subjects: Is the study necessary and can the research be done without the use of human subjects? There now exists a significant body of scientific evidence that warrants and justifies warning women not to use marijuana products at pre-conception, while pregnant, or breast-feeding. The University of Washington study is not necessary to conclude that marijuana use is associated with risk to the child (and also the mother). The National Academies, a lead authority, concluded in a scientific literature review in 2017: There is substantial evidence of a statistical association between maternal cannabis smoking and lower birth weight of the offspring. Studies have already shown that prenatal use is associated with a 50 percent increased likelihood of low birth weight. The Surgeon General's advisory of August 29, 2019 is also relied upon here. What is the "necessity" that this study addresses? The conclusion has already been made by the findings of science – pregnant women should refrain from marijuana use in order to protect the life and health of their child.

Yet, in spite of existing scientific literature of concern, a highly misleading recruitment statement appears on the University of Washington study's website introductory page: "**We do not expect to find anything of medical concern during the infant MRI scans**...If you're interested in helping us learn more about whether cannabis is safe to use for morning sickness, click the Sign Up button and let us know!"

Their lack of concern about the potential for adverse medical outcomes directly contradicts the findings of Grewen et al. (2015) which similarly evaluated postnatal outcomes using MRI scans on infants that had been exposed to marijuana in utero. As compared to controls, the exposed infants showed hypoconnectivity between brain regions: " Marijuana-specific differences were observed in insula and three striatal connections: anterior insula–cerebellum, right caudate–cerebellum, right caudate–right fusiform gyrus/inferior occipital, left caudate–cerebellum. +MJ neonates had hypo-connectivity in all clusters compared with −MJ and CTR groups." While an imperfect study because the cases included a proportion of women in the case group who used not only marijuana but also alcohol, tobacco, opiates and SSRIs, one of the two control groups was matched to the cases for use of those drugs, while the other was completely drug free. Notably, work in an animal model by Tortoriello et al. (2014) presents a plausible mechanism for the observed effect of marijuana seen between cases and controls. The evidence points towards harm, and could easily be followed up in an animal model that parallels the intent of the University of Washington study.

Furthermore, the ethics are clearly different between the Kleinhans et al. and Grewen et al. studies, because unlike the protocol for the former, the study of Grewen et al. did not recruit women while the fetus was developing but recruited while they were in neonatal care. Being unaware of marijuana use until the time of birth, the researchers could not intervene to encourage abstinence for the sake of the

fetus, whereas the University of Washington team could intervene, but their protocols do not allow them to. As a further point of distinction, the University of Washington protocol states that infants enrolled in the study will be screened and excluded if they have been in an NICU for 24 hours. This will, for obvious reasons, result in a biased outcome in reporting overall harm from marijuana use during pregnancy.

Typical morning sickness affects up to 91% of pregnancies (Castillo and Phillippi, 2015), and is regarded by many medical practitioners as being a reflex protecting against consumption of dangerous foods or beverages, as well as a sign of a healthy pregnancy because the absence of morning sickness is associated with a higher rate of miscarriage (reviewed by Sherman and Flaxman, 2002). The rare condition when morning sickness becomes pathologic, hyperemesis gravidarum, affects on average 1.1% of pregnancies, and is defined as a loss of 5% or more of the pre-pregnancy weight (Castillo and Phillippi, 2015). Maintenance of fluid and electrolyte balance may become problematic in this situation and pharmacologic intervention may become necessary, both for the health of the mother and the baby. To date, the serious documented outcomes include an increased risk for preterm births and low birth weight (Dodds et al., 2006).

Thus, if the Kleinhans study were to be proposing to recruit only those with hyperemesis gravidarum, the ethics might be more favorable. They would, however, have to exclude women whose marijuana use may have triggered the hyperemesis, which does occur in a subset of pregnant users (Alaniz et al., 2015). The study recruitment website is definitely remiss in not making that possibility clear to those interested in enrolling, and the research protocol describes no effort to ascertain if marijuana might be triggering hyperemesis in their study subjects.

In summary, there is already sufficient scientific evidence to answer the question as to whether or not marijuana is safe to use for typical morning sickness. That answer is no. Please see additional references for numerous research publications showing harm at the end of this letter.

Complaints have been filed with NIDA, The University of Washington, The World Medical Association regarding the Helsinki Declaration, The Office of Human Research, and two doctors have filed a human rights complaint on behalf of the children involved. Complaint documents will be forwarded on request.

Thank you for your time in reviewing this serious situation.

Best regards,

Pamela McColl
Child Rights Activist

Cynthia Walsh, M.A.,J.D.
Certified in Health Care Ethics
Alamosa, Colorado, USA

Anne Hassel P.T.
(Former employee in a marijuana dispensary selling high potency THC to pregnant women)
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Correspondence with the OHRP in regards to the University of Washington study began in September of 2019. On October an email was received from the OHRP to Pamela McColl:

October 25, 2019
Hello,
OHRP has reviewed the study and will not be opening a case.
Sincerely,
Division of Compliance Oversight OHRP

September 25, 2019

"OHRP is now reviewing your complaint and this study. We are currently gathering the information about the research being conducted before a full review is started. Once OHRP completes a full review of the study, the research conducted and the study's approval process, we will contact you with our findings. Please remember, this does not mean you can't contact OHRP again before we finish the full review. You can contact us using this email address to update your complaint at any time.
Thank-you,
Division of Compliance Oversight (OHRP)

September 17, 2019

Thank you for contacting the Office for Human Research Protections (OHRP).
OHRP has responsibility for oversight of compliance with the U.S. Department of Health and Human Services (HHS) regulations for the protection of human research subjects (see 45 CFR Part 46 at www.hhs.gov/ohrp/regulations-and-policy/guidance/index.html
In carrying out this responsibility, OHRP reviews allegations of noncompliance involving human subject research projects conducted or supported by HHS or that are otherwise subject to the regulations, and determines whether to conduct a for-cause compliance evaluation. For further details see OHRP's guidance, "Compliance Oversight Procedures for Evaluating Institutions,''
at www.hhs.gov/ohrp/compliance-and-reporting/evaluating-institutions/index.html.
OHRP has jurisdiction only if the allegations involve human subject research (a) conducted or supported by HHS, or (b) conducted at an institution that voluntarily applies its Assurance of Compliance to all research regardless of source of support. Since this requirement appears to be met by the circumstances described in your email, OHRP appears to have jurisdiction.

Sincerely,
Division of Compliance Oversight

cc. Surgeon General Jerome Adams

cc. Director NIDA Dr. Nora Volkow

In-text citations:

Alaniz VI, Liss J, Metz TD, Stickrath E. Cannabinoid hyperemesis syndrome: a cause of refractory nausea and vomiting in pregnancy. Obstet Gynecol. 2015 Jun;125(6):1484-6.

Castillo MJ, Phillippi JC. Hyperemesis gravidarum: a holistic overview and approach to clinical assessment and management. J Perinat Neonatal Nurs. 2015;29(1):12-22.

Dodds L, Fell DB, Joseph KS, Allen VM, Butler B. Outcomes of pregnancies complicated by hyperemesis gravidarum. Obstet Gynecol. 2006;107(2, pt 1):285–292.

Grewen K, Salzwedel AP, Gao W. Functional Connectivity Disruption in Neonates with Prenatal Marijuana Exposure. Front Hum Neurosci. 2015;9:601.

Sherman PW, Flaxman SM. Nausea and vomiting of pregnancy in an evolutionary perspective. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S190-7.

The National Academies of Sciences, Engineering, and Medicine, 2017, The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. National Academies Press, Washington, D.C. 20001

Tortoriello G, et al. Miswiring the brain: Δ9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway. EMBO J. 2014;33(7):668-85.

Additional references on specific neonatal outcomes:

Lower birth weight, animal studies

Benevenuto SG et al., ***Recreational use of marijuana during pregnancy and negative gestational and fetal outcomes: An experimental study in mice***. Toxicology. 2017;376:94-101.

> "Five minutes of daily (low dose) exposure during pregnancy resulted **in reduced birthweight**.....females from the Cannabis group presented reduced maternal net body weight gain, despite a slight increase in their daily food intake compared to the control group"

Lower birth weight, human studies

Gunn,JKL, Rosales CB, Center KE, Nunez A, Gibson SJ, Christ C, and Ehiri EJ. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open* 2016; 6(4):e009986.

> "Infants exposed to cannabis in utero had a decrease in birth weight (low birth weight pOR=1.77: 95% CI 1.04 to 3.01; pooled mean difference (pMD) for birth weight=109.42 g: 38.72 to 180.12) compared with infants whose mothers did not use cannabis during pregnancy. Infants exposed to cannabis in utero were also more likely to need placement in the neonatal intensive care unit compared with infants whose mothers did not use cannabis during pregnancy (pOR=2.02: 1.27 to 3.21)."

Brown SJ, Mensah FK, Ah Kit J, Stuart-Butler D, Glover K, Leane C, Weetra D, Gartland D, Newbury J, Yelland J. Use of cannabis during pregnancy and birth outcomes in an Aboriginal birth cohort: a cross-sectional, population-based study. BMJ Open. 2016;6(2):e010286.

> "Controlling for education and other social characteristics, including stressful events/social health issues did not alter the conclusion that mothers using cannabis experience a higher risk of negative birth outcomes (adjusted OR for odds of low birth weight 3.9, 95% CI 1.4 to 11.2)."

Fergusson, D. M., L. J. Horwood, and K. Northstone. 2002. Maternal use of cannabis and pregnancy outcome. British Journal of Obstetrics and Gynaecology 109(1):21–27.

"Over 12,000 women expecting singletons at 18 to 20 weeks of gestation who were enrolled in the Avon Longitudinal Study of Pregnancy and Childhood……the babies of women who used cannabis at least once per week before and throughout pregnancy were 216g lighter than those of non-users."

Preterm birth, animal studies

Wang H, Xie H, Dey SK. Loss of cannabinoid receptor CB1 induces preterm birth. PLoS One. 2008;3(10):e3320.

"CB1 deficiency altering normal progesterone and estrogen levels induces preterm birth in mice…. CB1 regulates labor by interacting with the corticotrophin-releasing hormone-driven endocrine axis."

Preterm birth, human studies

Luke S, Hutcheon J, Kendall T. Cannabis Use in Pregnancy in British Columbia and Selected Birth Outcomes. J Obstet Gynaecol Can. 2019;41(9):1311-1317.

"Using cannabis in pregnancy was associated with a 47% increased risk of SGA (adjusted OR 1.47; 95% CI 1.33–1.61), a 27% increased risk of spontaneous preterm birth (adjusted OR 1.27; 95% CI 1.14–1.42), and a 184% increased risk of intrapartum stillbirth (adjusted HR [aHR] 2.84; 95% CI 1.18–6.82)."

Corsi DJ, Walsh L, Weiss D, Hsu H, El-Chaar D, Hawken S, Fell DB, Walker M. Association Between Self-reported Prenatal Cannabis Use and Maternal, Perinatal, and Neonatal Outcomes. JAMA. 2019;322(2):145-152.

"In a cohort of 661 617 women…. The crude rate of preterm birth less than 37 weeks' gestation was 6.1%among women who did not report cannabis use and 12.0% among those reporting use in the unmatched cohort (RD, 5.88% [95%CI, 5.22%-6.54%]). In the matched cohort, reported cannabis exposure was significantly associated with an RD of 2.98%(95%CI, 2.63%-3.34%) and an RR of 1.41 (95% CI, 1.36-1.47) for preterm birth. Compared with no reported use, cannabis exposure was significantly associated with greater frequency of small for gestational age (third percentile, 6.1% vs 4.0%; RR, 1.53 [95%CI, 1.45-1.61]), placental abruption (1.6%vs 0.9%; RR, 1.72 [95% CI, 1.54-1.92]), transfer to neonatal intensive care (19.3%vs 13.8%; RR, 1.40 [95%CI, 1.36-1.44]), and 5-minute Apgar score less than 4 (1.1% vs 0.9%; RR, 1.28 [95%CI, 1.13-1.45])."

Saurel-Cubizolles MJ, Prunet C, Blondel B. Cannabis use during pregnancy in France in 2010. BJOG. 2014;121(8):971-7.

"Cannabis users had higher rates of spontaneous preterm births: 6.4 versus 2.8%, for an adjusted odds ratio (aOR) of 2.15 (95% CI 1.10–4.18)."

Leemaqz SY, Dekker GA, McCowan LM, Kenny LC, Myers JE, Simpson NA, Poston L, Roberts CT; SCOPE Consortium. Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not other common late pregnancy complications. Reprod Toxicol. 2016;62:77-86.

> "continued maternal marijuana use at 20 weeks' gestation was associated with'' spontaneous preterm birth "independent of cigarette smoking status [adj OR2.28 (95% CI:1.45–3.59)] and socioeconomic index (SEI) [adj OR 2.17 (95% CI:1.41–3.34)]. When adjusted for maternal age, cigarette smoking, alcohol and SEI, continued maternal marijuana use at 20 weeks' gestation had a greater effect size [adj OR 5.44 (95% CI 2.44–12.11)]."

Impacts on the neonatal immune system, animal study

Zumbrun EE et al. Epigenetic Regulation of Immunological Alterations Following Prenatal Exposure to Marijuana Cannabinoids and its Long Term Consequences in Offspring. J Neuroimmune Pharmacol. 2015; 10(2):245-54.

> "Data from various animal models suggests that in utero exposure to cannabinoids results in profound T cell dysfunction and a greatly reduced immune response to viral antigens

Impacts on cortical wiring and development, animal studies

Tortoriello G, et al. Miswiring the brain: Δ9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway. EMBO J. 2014;33(7):668-85.

> "Here, we show that repeated THC exposure disrupts endocannabinoid signaling, particularly the temporal dynamics of CB1 cannabinoid receptor, to rewire the fetal cortical circuitry....these data highlight the maintenance of cytoskeletal dynamics as a molecular target for cannabis"

DiNieri JA, Wang X, Szutorisz H, Spano SM, Kaur J, Casaccia P, Dow-Edwards D, Hurd YL. Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. Biol Psychiatry. 2011 Oct 15;70(8):763-9.

> "we exposed pregnant rats to THC and examined the epigenetic regulation of the NAc Drd2 gene in their offspring at postnatal day 2, comparable to the human fetal period studied, and in adulthood…. Decreased Drd2 expression was accompanied by reduced D2R binding sites and increased sensitivity to opiate reward in adulthood"

Rodríguez de Fonseca F, Cebeira M, Fernández-Ruiz JJ, Navarro M, Ramos JA. Effects of pre- and perinatal exposure to hashish extracts on the ontogeny of brain dopaminergic neurons. Neuroscience. 1991;43(2-3):713-23.

> "Perinatal exposure to cannabinoids altered the normal development of nigrostriatal, mesolimbic and tuberoinfundibular dopaminergic neurons, as reflected by changes in several indices of their activity".

Impacts on cortical wiring and development, human studies

Grewen K, Salzwedel AP, Gao W. Functional Connectivity Disruption in Neonates with Prenatal Marijuana Exposure. Front Hum Neurosci. 2015;9:601.

> "+MJ (marijuana-exposed) neonates had hypo-connectivity in all clusters compared with –MJ (marijuana unexposed) and CTR (control) groups. Altered striatal connectivity to areas involved in visual spatial and motor learning, attention, and in fine-tuning of motor outputs involved in movement and language production may contribute to neurobehavioral deficits reported in this at-risk group. Disrupted anterior insula connectivity may contribute to altered integration of interoceptive signals with salience estimates, motivation, decision-making, and later drug use."

El Marroun H, Tiemeier H, Franken IH, Jaddoe VW, van der Lugt A, Verhulst FC, Lahey BB, White T. Prenatal Cannabis and Tobacco Exposure in Relation to Brain Morphology: A Prospective Neuroimaging Study in Young Children. Biol Psychiatry. 2016;79(12):971-9.

> "prenatal cannabis exposure was associated with differences in cortical thickness….. it may be possible that the frontal cortex in cannabis-exposed children undergoes altered neurodevelopmental maturation (i.e., having differences in cortical trajectories) as compared with nonexposed control subjects"

Wang X, Dow-Edwards D, Anderson V, Minkoff H, Hurd YL. In utero marijuana exposure associated with abnormal amygdala dopamine D2 gene expression in the human fetus. Biol Psychiatry. 2004; 56:909–915.

> "Adjusting for various covariates, we found a specific reduction, particularly in male fetuses, of the D(2) mRNA expression levels in the amygdala basal nucleus in association with maternal marijuana use. The reduction was positively correlated with the amount of maternal marijuana intake during pregnancy."

Added post letter: Archives of Toxicology (2019) 93:179–188 https://doi.org/10.1007/s00204-018-2322-9 GENOTOXICITY AND CARCINOGENICITY Low doses of widely consumed cannabinoids (cannabidiol and cannabidivarin) cause DNA damage and chromosomal aberrations in human-derived cells.