**Editor’s name**

**Editor, Traffic Injury Prevention**

**Re: GCPI-2020-0118**

**June 16, 2020**

Please find enclosed the revised manuscript GCPI-2020-0118, entitled “Impact of Cannabis and Low Alcohol Concentration on Divided Attention Tasks during Driving” and our point by point response to the reviewers’ comments. We appreciate the thorough review and insightful feedback. Our responses immediately follow the comment/suggestion and are in italics. We believe the manuscript is strengthened and hope it is now acceptable for publication.

**Comments from Reviewer #1**

This is an interesting paper on the impact of THC and low levels of alcohol on driving performance during divided attention conditions. Overall the paper is of interest, but also raises some issues that the authors should address.

1. The authors state that participants inhaled 500 mg placebo (0.008±0.002% THC), low THC (2.9±0.14%), or high THC (6.7±0.05%) vaporized cannabis. However, the authors should also state the actual amount of THC that was administered in both THC conditions. That will increase comparability with other studies in the field.

*As suggested, we added the mg THC in the cannabis cigarette in the Dosing subsection in addition to the percentages. However, we also added text to clarify the connection between the THC in the cigarette and blood THC. Participants inhaled ad libitum over 10 minutes, making the amount of THC reaching the blood dependent upon an individual’s inhalation rate, depth, hold time, exhalation rate and number of puffs, hence the importance of having blood concentrations throughout the study. Previous research demonstrated substantial interindividual variability in cannabinoid concentration profiles under any dosing conditions (Desrosiers 2014, Hartman 2015, Newmeyer 2016). This is why we focus on blood concentrations rather than the administered or inhaled amounts of THC.*

1. Only 19 out 55 participants actually completed the study, What were the reasons for the large number of drop-outs?

*As suggested, we added the following sentence to the Participants subsection “Reasons for noncompletion were predominantly personal owing to the rigorous nature of the data collection protocol over 7 in-person visits with 10-16 hour overnight stays; however, some withdrew due to nausea and/or emesis from simulator sickness or perhaps in response to the inhaled cannabis.” In studies with illicit substance users and high demand schedules, higher dropout rates are typical, as seen in Dr. Huestis’ controlled administration studies at the National Institute on Drug Abuse (Desrosiers 2014, Hartman 2015, Newmeyer 2016).*

1. The authors used modeling to associate driving performance while performing a secondary task while under the influence of THC and alcohol. This approach raises two questions that should be discussed. First, duration of the secondary tasks were very short. The side mirror task lasted for 70 sec (across 14 trials), the artist search task lasted 30 secs (across 3 trials) and the message reading task lasted 60 secs (across 6 trials). In essence, these secondary data sets represent less than 2 minutes of a driving test that in total lasted 45 minutes. That really raises the question how representative and replicable these data actually are. The number of trials are extremely low and one wonders what the test-retest reliability of these data actually are. If would strengthen the current findings if the authors would provide test-retest correlations for driving parameters during secondary task performance. Second, BAC and THC were not actually assessed during these secondary task trials but modeled. It is not clear how this modelling actually occurred. It would be helpful if the modelling was described in more detail, and indicators of the strengths/reliability of modeling were provided.

*As suggested, we added supplemental model information to the Appendix that includes variance components and intraclass correlations (ICC) of the repeated measures for the various outcome measures we considered, which are estimated via the variance components of our models. Lower ICCs are desirable from a statistical perspective given limitations on the number of task repeats we can include in the study. Also, the reviewer indicates that the trials are only 2 minutes of the 45-minute drive; however, the actual times including the repeats and a suitable washout period is much more than 2 minutes. The actual time is side mirror task 70 sec x 14 trials or 16.3 minutes, artist search 30 sec x 3 trials or 1.5 minutes, and message reading task 60 sec x 6 trials or 6 minutes; together the tasks comprise 23.9 minutes of the 45-minute drive. In between repeats, they also were busy driving, listening to navigation instructions, watching for pedestrian and animal roadway intrusions, avoiding other cars, heeding traffic signals etc. In response to the second part of the comment, collecting blood during the driving would be artificial and distracting from the driving task. Blood THC was collected immediately prior and following the drive and concentrations during the drive were modeled via individual power-curve regression on the pre-drive (0.17 and 0.42h) and post-drive (1.4 and 2.3h) specimens. BrAC concentrations during drives were modeled by linear interpolation, as alcohol was in the post-absorptive phase, during which its pharmacokinetics are linear (Jones and Andersson, 2003). As suggested, we included this information in the Data Collection subsection and directed readers to Hartman et al. 2016a, the primary blood pharmacokinetics manuscript, and Hartman 2015 for more detailed information on the blood modeling.*

1. It is not always clear whether driving performance (ie lane departures, SDLP, speed etc) significantly differed during secondary task performance as compared to the control intervals, or between THC/BAC and placebo conditions. Perhaps the authors could elaborate?

*As suggested, we added clarifying text detailing that the only significant difference we observed was decreased speed while engaged in the message reading task. Analyses were not performed by condition per se, as condition was accounted for in the statistical models by blood THC concentration and BrAC. This information can be found in Table 2 of the results section. Other non-significant differences between task and control intervals are also shown in Table 2.*

**Comments from Reviewer #2**

The manuscript describes the impact of cannabis and low alcohol concentration on driving performance. The manuscript is very interesting and fits into the current needs. The problems presented are on time. The still increasing marijuana use has created a demand for such research. The project seems very wide and well developed. The article is well written and although I read it twice carefully, I don't have many comments.

1. Page 3, line 20 and page 5, line 38 – the authors should present time intervals in minutes instead of hours or just add the minutes in brackets. It will be clearer then; 0.17 hour is 10 minutes, and 0.42 hour is 25 minutes.

*As suggested, we revised the text in this location to report minutes rather than hours.*

1. Page 3, line 43 – I am not sure if keywords “Cannabis” and “Marijuana” have to start with capital letters.

*To our knowledge, keywords should be capitalized when listed as keywords, but not when appearing in the text of the manuscript.*

1. Page 4, line 52 – why authors wrote here that participants aged 21-55 while on page 7 (line 17) the participants aged 21-37? I suspect that the data on page 3 applies to all participants in all experiments and on page 7 to those 19 participants that completed study covered by the presented manuscript. In my opinion, the data on participants should only apply to those to whom the results presented here are related. Why 36 enrolled adults did not complete the study?

*The first age range (21-55) is part of the inclusion criteria for recruitment of participants, while the second age range (21-37) describes the actual range of participants who completed the study. This is the standard required presentation of data in human studies. As suggested, we added the following sentence to the Participants subsection in the Results to address the 36 enrolled adults who did not complete the full study*. “*Reasons for noncompletion were predominantly personal owing to the rigorous nature of the data collection protocol over 7 in-person visits with 10-16 hour overnight stays; however, some withdrew due to nausea and/or emesis from simulator sickness or perhaps in response to the inhaled cannabis.” In studies with illicit substance users and high demand schedules, higher dropout rates are typical, as seen in Dr. Huestis’ controlled administration studies at the National Institute on Drug Abuse.*

1. Page 11, lines 20 and 43 (references 4 and 10) – in most references the full name journals are presented but in these two only titles abbreviations.  Page 11, line 20 (reference 4) – between journal title and between issue number and page numbers should be comma (not dot and colon). Page 12, line 11 (reference 16) – the year number should not be in brackets.

*As suggested, we revised the references to include the full journal names, we replaced the dots and colons with commas, and we removed the brackets around year in the 16th reference.*

1. Figure 1 – why subjects with placebo/placebo and placebo/alcohol have THC concentrations even up to over 5 ng/mL? This seems pretty much for occasional users who have not taken marijuana for over a week. Some concentrations in High THC subjects are even lower than in Placebo group. It would be very good to explain the reason for this in the text.

*As suggested, we added text to the Dosing subsection in the results. “Residual THC was detected in some completers—up to 6.3 ng/mL at baseline— indicating inconsistency in self-reported frequency of intake; Hartman et al. 2016a provides further discussion.” The within-subject design of this study helps mitigate the residual THC concentrations, as all individuals are compared to themselves across sessions.*

1. Table 2 - what means three dots at “<0.001” in the “Message-Riding/ Speed” line and “p-values” column. It should be explained below Table.

*As suggested, we added an explanation of the code in the table legend. We utilized this symbol to draw attention to p-values below 0.001.*

Overall, I think this article is very well-done.

**Comments from Reviewer #3**

The paper reports a simulator study on cannabis and driving performance. The influence of alcohol is in focus. The study is much needed and performed at a high level of expertise. The model produces weak results on the influence of cannabis and alcohol on the driving skills.

1. Given the commonly accepted fact that alcohol influence your driving skills in a non-acceptable way it would be of value to comment how sensitive this model is to document that. Is your experimental model valid?

*Our analyses detected a significant negative effect of alcohol for multiple outcomes we considered, including SDLP in the message-reading task and lane departure durations in the side-mirror task. Considering alcohol levels were ~0.05% during the drive, and that task durations were relatively short, it is likely that some models were underpowered to detect the established detrimental effects of alcohol. We were careful to avoid interpreting this as alcohol not having negative effects. In addition, alcohol impaired performance on the primary outcome measures in Hartman 2015 and Hartman 2016c.*

1. You base your work and text on the relationship to THC blood concentration. Figure 1. Is used to demonstrate variability. However, the time point for sampling is in a very dynamic time point where THC concentrations are being rapidly declining. Therefore, I think your measurements are problematic to interpret.

*THC was quantified in blood four times after ad lib cannabis smoking and blood THC concentrations were individually modeled throughout driving via individual power-curve regression, an approach discussed in greater detail in Hartman et al. 2015. As suggested, we added text to the Data Collection subsection, including a statement directing readers to Hartman. 2015 and Hartman 2016a for more detailed information on the modeling. Additionally, the within subject-design, which allows each individual participant to serve as their own control, helps address these issues because even though the actual numbers might be changing rapidly during the drive, participants are being compared to themselves. Hartman et al. 2015 discusses the consistency of measurements within subjects across sessions at the same cannabis dose.*

1. Also, you seem to assume that blood concentrations of THC are golden standard for effect relationship (as for alcohol). I would challenge this as THC blood concentrations cannot representative due to the rapid redistribution to tissue and brain where effect occurs.

*Blood THC concentrations are the closest marker we have available to the brain in living subjects except for brain imaging, but we are well aware of the lack of correlation between THC concentrations and drug impaired driving, as noted in our publications Huestis 2015a, Huestis 2015b, Hartman 2016a and Hartman 2016b. However, blood THC is the most relevant and applicable metric for DUID. Suspected drugged drivers most typically have blood collected, because across drug classes (including but not limited to cannabinoids) blood is generally the closest available marker. In that sense, it is something of a gold standard—not necessarily for ideal effect relationship, but for study and analysis of drugged driving.*

1. Please speculate how representative and useful the THC blood concentrations are.

*The blood THC concentrations document the onset, peak and duration of THC concentrations in each individual and document that the controlled cannabis administration occurred. While THC concentrations peak during cannabis inhalation, there is a time delay in peak cannabinoid effects. Blood THC concentrations are the closest marker we have available to the brain in living subjects except for brain imaging, but we are well aware of the lack of correlation between THC concentrations and drug impaired driving, as noted in our publications Huestis 2015a, Huestis 2015b, Hartman 2016a and Hartman 2016b. We measured driving performance in the same individuals under placebo, low dose alcohol, low dose THC, high dose THC, and low dose alcohol plus low dose THC, and high dose THC and low dose alcohol. Also, since we had this excellent study design, we were able to show that people titrate their cannabis dose and we were able to collapse the low and high THC doses into just active THC, increasing our statistical power. We also were able to show how rapidly THC concentrations decrease after documented driving impairment and discussed at length the potential impacts on interpretation (Hartman 2016a).*

1. Introduction, first sentence. You mean in suspected DUI:s?

*The reviewer is correct; we modified the text to clarify this statement, which is based upon the research of Augsburger et al. 2005 and Berning et al. 2015 (complete references given in the appendix). Because we are limited to 20 references in the main text, we did not have room to include these citations.*

1. Please add a reference to your used simulator model.

*As suggested, we added a hyperlink to the NADS-1 website (https://www.nads-sc.uiowa.edu/sim\_nads1.php) to the Data Collection subsection. This official page describes the simulator in greater detail.*

1. Regarding THC concentrations again. Your statement should include a reflection on how representative these are in an investigation after an accident. Problematic parameter!

*The THC blood concentrations in this study cover concentrations found in DUID investigations and in postmortem motor vehicle crashes. These individual profiles reflect THC blood concentrations from before and up to 8.3 hours after cannabis inhalation. Of course, there are different blood concentrations found in individuals later after consuming cannabis. Again, Hartman 2016a—also generated from this study—thoroughly expounds upon this issue and its implications. We also reported in many other controlled administration studies THC concentrations at longer periods after cannabis intake.*

1. THC measurements. Add some information regarding measurement uncertainty.

*Measurement uncertainty was not included in this human controlled cannabis administration study. Uncertainty of measurement is different in every laboratory and is included in forensic toxicology results.*

1. Results. Rather than using single concentration value did you consider using AUD values for analysis, which might be more relevant as exposure parameter?

*Assuming the reviewer is referring to AUC, we did not consider AUC values as the field of DUID uses blood concentrations and in actual cases multiple specimens are not obtained. Furthermore, as stated earlier, individuals titrate their dose by controlling their topography. We were able to collapse all data into one for the active low and high THC doses.*

1. In the Appendix tables explain the subgroups: Urban, Interstate, Rural.

*As suggested, we added the following text to explain the different drive segments in the Appendix tables (A1 and A3) that reference the drive segments:* “*Urban segments involved a two-lane city roadway with posted speed limits between 40-72 km/h; Interstate segments involved a four-lane divided expressway with a posted speed limit of 112 km/h; Rural segments involved two-lane undivided roads with curves, and gravel portions.”*

**Comments from Reviewer #4**

This manuscript is describing the effects of cannabis with/without alcohol compared to placebo on driving simulated tasks to explore the effects on driving safety in healthy white males (within-subject) individuals age 21-37 (n=19), using three divided attention tasks and three aspects of driving performance.  Outcomes were modeled using linear regression in response to THC or BrAC.  This is an important preliminary investigation of the combinatorial effects of THC and alcohol. As with other studies, blood concentrations of THC were highly variable across subjects.   Figure 1 (Table A1) visualizes the THC blood levels with or without co-alcohol administration.

1. It would be interesting to see statistical analysis on these values, as low THC/etOH seems to have a trend for reduced blood levels compared to THC/placebo, while high THC/etOH seems to have a trend for higher blood levels.  Do you have any explanation for these effects?  or why in two subjects the levels decreased significantly?

*In general, we observed higher variability (and higher medians) in THC concentrations following alcohol in comparison to the same doses without alcohol. Given the space limitations of this manuscript we are unable to provide an in-depth analysis exploring this aspect of the data in this paper; however, such an analysis was performed in the citations Hartman et al. 2015 and Hartman et al. 2016 that addresses the interesting patterns that the reviewer mentions.*

1. Was there any change in scoring based on urban vs. rural scenarios?

*We did not alter any of our outcome measures in response to the different drive scenarios. However, for tasks where some instances could take place in differing drive segments, we adjusted for task location in our statistical models. In response to the reviewer’s comment, we modified the text in the final paragraph of the Statistical Analyses subsection to better describe this.*

1. The dose of THC is quite low compared to what young men are typically accessing in 'real world' cannabis use.  Can you please add a sentence or two to address this?

*As suggested, we added the following to the Discussion section: “Although the cannabis in this study had a lower potency than typically observed in seized materials, this is not a substantial limitation, as individuals inhaling cannabis can self-titrate their dose to the subjective experience and the tachycardia they are comfortable with, producing similar blood concentrations across a wide range of cannabis potencies. The high-THC cannabis concentrates such as hashish are difficult to administer for safety and ethical reasons.”*

**References Cited in the Response**

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2. Hartman RL, Brown TL, Milavetz G, Spurgin A, Pierce RS, Gorelick DA, Gaffney G, Huestis MA. Cannabis Effects on Driving Lateral Control With and Without Alcohol. *Drug Alcohol Dependence*. 2015 Sep 1;154:25-37.
3. Huestis MA. Cannabis-Impaired Driving: A Public Health and Safety Concern. *Clinical Chemistry.* 2015a Oct;61(10):1223-5.
4. Huestis MA. Deterring Driving Under the Influence of Cannabis. *Addiction*. 2015b Nov;110(11):1697-8.
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6. Hartman RL, Richman JE, Hayes CE, Huestis MA. Drug Recognition Expert (DRE) Examination Characteristics of Cannabis Impairment. *Accident Analysis Prevention.* 2016b Jul;92:219-29.
7. Hartman RL, Brown TL, Milavetz G, Spurgin A, Pierce RS, Gorelick DA, Gaffney G, Huestis MA. Cannabis Effects on Driving Longitudinal Control With and Without Alcohol. *Journal Applied Toxicology* 2016c Nov;36(11):1418-29.
8. Newmeyer MN, Swortwood MJ, Barnes AJ, Abulseoud OA, Scheidweiler KB, Huestis MA. Free and Glucuronide Whole Blood Cannabinoids’ Pharmacokinetics after Controlled Smoked, Vaporized and Oral Cannabis Administration in Frequent and Occasional Cannabis Users: Identification of Recent Cannabis Intake. *Clinical Chemistry* 2016 Dec;62(12):1579-1592.