UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

January 13, 2023

MEMORANDUM

SUBJECT: Science and Ethics Review of a Protocol for Efficacy Testing of SCJ Personal Repellent Products against Mosquitoes in a Field Study

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REF: S.C. Johnson & Son protocol for "Efficacy Testing of SCJ Personal Repellent Products against Mosquitoes in a Field Study." Protocol ID: 90020741. February 2022.

SCJ has submitted a protocol to the EPA for field testing of two skin-applied repellents, one an aerosol product (EPA registration number 4822PA51; DP 465257) containing 10% p-menthane-3,8-diol (PMD) and the other a solid stick product (EPA registration number 4822PA52; DP 465253) containing 10% picaridin, against wild populations of representative

mosquito vectors, from both scientific and ethical perspectives. This review assesses the scientific aspects of the proposed research for a product performance study to evaluate the efficacy of skin applied insect repellents in terms of the recommendations of EPA Guideline *OPPTS 810.3700: Insect Repellents to be Applied to Human Skin*[1], concerning scientific merit of the proposed study. Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L and the recommendations of the Human Studies Review Board (HSRB).

If the protocol is revised to address the recommendations outlined in this review, the resulting research is likely to meet applicable scientific and ethical standards for research with human subjects.

A. Completeness of Protocol Submission

The submitted protocol package, additional information on statistical justification for the proposed sample size, and supplementary documentation of review by the WCG Institutional Review Board (IRB) were reviewed for completeness against the required elements listed in 40 CFR §26.1125. The EPA's protocol review (Attachment 1) and ethics submission checklist (Attachment 2) document how the submission complies with the regulatory requirements for protocols describing research with human subjects. With the EPA's recommendations outlined in this memo addressed, the submission will be complete.

B. Summary Assessment of Science Aspects of the Proposed Research

Objectives

The primary objective of the protocol is to determine the duration of efficacy of two separate personal repellent products (an aerosol spray containing 10% PMD and a solid stick containing 10% picaridin as the active ingredient) against wild mosquitoes that have the potential to transmit pathogens of public health importance in a field setting using human test subjects (p. 2). The human test subjects will be representative of the target populations for these products, which is the typical user of skin-applied repellents against mosquitoes in the United States.

Efficacy Endpoints

Efficacy will be measured as the duration between the time the test substance is applied and the time the first confirmed mosquito landing on a test subject's treated appendage occurs which will be defined as the complete protection time (CPT). The first confirmed landing (FCL), which is the endpoint of the study for each treated test subject, is defined as the time at which one mosquito landing occurs and a second landing occurs within 30 minutes. The second landing confirms the first landing. The CPT data points for each individual will be statistically analyzed to determine a median complete protection time (mCPT) for each individual repellent at each test site separately.

[1]EPA. Product Performance Test Guidelines; OPPTS 810.3700: Insect Repellents Applied to Human Skin. EPA 712-C-10-001. July 7, 2010. https://www.regulations.gov/document/EPA-HQ-OPPT-2009-0150-0011

Study Design

The protocol will utilize human test subjects to determine the efficacy of two repellent products, a 10% PMD aerosol spray and a 10% picaridin solid stick, against specific vectors encountered at field test sites. The protocol specifies 14 treated test subjects per product per location (p. 25). The registrant's rationale for using 14 treated test subjects versus the EPA's suggested 13 is that: "[1] *it is usually desirable to have a sample size that is even to allow for an equal number of male and female test subjects* and, [2] *the 95% lower confidence limit of the Kaplan-Meier median is the 3rd smallest value when the sample size is 14 but the 2nd smallest value when the sample size is 13, so a sample size of 14 is likely to give a more precise low-end estimate of the median*." (Attachment 3) The proposed testing will determine a mCPT for each product at two ecologically distinct testing sites where the three required representative *Aedes*, *Anopheles*, and *Culex* species are present. The Agency requires the presence of these three representative species between sites, but all three do not have to be present at each testing site. A standard application rate of 1.0 g/600 cm^2 that is derived from dosimetry data on spray products[2] will be used for the PMD aerosol spray (p. 16). Dosimetry testing will be conducted with the 10% picaridin stick at the laboratory screening and training facility or at a designated field site prior to field efficacy evaluation to determine the typical consumer rate to be used during field efficacy trials (pp. 26-27).

Potential test subjects will be selected based on criteria listed in Section IX of the protocol (pp. 3-4) to ensure that subjects are qualified to participate in the study. To be included in the study a subject must: be able to prove that they are between 18-55 years of age with valid identification, read and understand English, not be an employee of SC Johnson or an immediate family member, have reliable transportation to and from the test site and training location, be willing to be exposed to and potentially bitten by mosquitoes, refrain from the use of alcohol 12 hours before testing, refrain from nicotine and fragrance products like cologne during testing, be willing to sign the informed consent document (ICD), be willing to have body temperature checked as part of COVID protocols, and be a user of insect repellent products. Individuals will be omitted from the study if they suffer from specific physical ailments that would potentially endanger them during participation, such as asthma, skin problems, or sensitivity or allergy to mosquito bites. Pregnant and lactating women will be excluded from participation. Individuals that provide consent by signing the ICD will be considered as enrolled in the study. However, only those that subsequently demonstrate they are attractive to mosquitoes and successfully complete aspirator training will be eligible to participate in efficacy testing in the field.

A subject training session that includes attractiveness testing, training on using an aspirator to capture mosquitoes, measuring subjects' limbs, and conducting a dose determination (dosimetry) study for the picaridin product, is projected to take 2-3 hours and will occur within 2 months prior to the start of product field testing (p. 9). This training session may be conducted in a laboratory or at a field site and the training will begin with attractiveness testing.

[2]Fuentes, C., Bohnenblust, E., Arling, M. Science and Ethics Review of a Protocol for Field Evaluation of Three Topically-Applied Insect Repellent Products Containing IR3535. https://www.epa.gov/sites/default/files/2017-07/documents/ir3535_protocol_science_and_ethics_review_6-29-17.pdf

Attractiveness testing conducted in the laboratory will consist of an individual inserting their untreated forearm through a cloth sleeve into a 2' x 2' x 2' test cage containing approximately 50 female lab-reared mosquitoes that have not taken a blood meal (p. 12). The proposed size of the cage is consistent with the OPPTS 810.3700 Guideline, Section (j), p. 27, but the recommended insect density in the Guideline is 200 mosquitoes per cage which is equivalent to 1 mosquito per 1,160 cm^3. The current description in the protocol is the equivalent of 1 mosquito per 4,640 cm^3 and no explanation is provided as to why a lower mosquito density will be used. An individual is deemed attractive if five landings occur in one minute or less during the laboratory attractiveness testing (p. 9). Individuals will have 3 attempts to confirm attractiveness before being excluded from further participation (p. 23). Any individual determined to be unattractive to mosquitoes (i.e., fewer than 5 landings within a one-minute exposure period after three tries) will not be permitted to participate any further with the study and will be financially compensated for their participation up to that point. Individuals deemed to be attractive to mosquitoes will be trained to identify when a mosquito has landed on their skin and how to capture mosquitoes with an aspirator before they are able to bite. For landing identification and aspirator training conducted in the laboratory an individual will insert their untreated forearm into a 2' x 2' x 2' test cage containing approximately 10 female lab-reared mosquitoes that have not taken a blood meal. A staff member will demonstrate the process first and then allow the individual to practice until that person and the study staff "*feels they are sufficiently proficient to participate in the field test*" (p.10).

Field site training in lieu of laboratory training is included in the protocol as an option, projected to take 2-3 hours. This training will occur within 2 months prior to the start of product efficacy testing in the field. Attractiveness testing conducted in the field will be evaluated where an individual will wear a bug suit (along with gloves and closed-toe shoes) which allows wild mosquitoes to land on an individual without being able to bite the person wearing the suit. The bug suit is described as a jacket and pants made of tightly woven breathable material (nylon) with a screened mesh covering over the face that allows for air exchange but is impenetrable to mosquito bites (pp. 9, 27). Each person will keep their bug suit on for the entirety of attractiveness training so that "*they will not expose any skin directly to mosquitoes*" (p. 9) and be considered attractive if there are five mosquito landings on their suit-covered forearm or lower leg within a five-minute exposure period. Individuals deemed to be attractive to mosquitoes will be trained to identify when a mosquito has landed on their bug suit-covered forearm or lower leg and how to capture them with an aspirator before they are able to bite or fly away. For landing identification and aspirator training conducted in the field an individual will practice observing and aspirating mosquitoes that have landed on their bug suit-covered limb until that person and the study staff feels they are sufficiently proficient with the aspirator needed to participate in the field test.

Test subjects will have their forearms and lower legs measured to determine the appropriate treatment area for the dosimetry testing either in the laboratory or at the field site and the appropriate treatment area for the individual dose application during field efficacy evaluation (described below in the *Estimation of Skin Surface Area* section). The details described in the protocol for treated area size and preparation (pp. 23-24) are similar to the parameters described in the OPPTS 810.3700 Guideline (Section (j), p. 28).

A dose determination test (dosimetry) for the 10% picaridin solid stick product will also be conducted in the laboratory or in the field on the subject training day (pp. 26-27). Test subjects will be asked to wash their designated arm or leg using a gentle, unscented soap. They will then dry their limb thoroughly with a paper towel, wipe it with a 70% solution of isopropanol or ethanol in water, and allow it to dry. Researchers will weigh the product, then provide the picaridin solid stick and labeling to the subjects and instruct them to apply the product as they normally would after reading the label instructions. After application, researchers will measure the amount applied by weighing the solid stick. Subjects will wash the treated arm and the same process will be repeated a total of 3 times, alternating which limb the subject treats for each test.

Field efficacy testing will occur at Brighton Dale Park in Kenosha County, Wisconsin and at Hale Reservation in Westwood, Massachusetts (Norfolk County). The protocol also suggested that alternative locations in the United States may be used if adequate mosquito density could not be found at the two named locations (p. 17) but did not list where these would be. Repellency evaluations will be conducted where each product is tested over the course of one day at each test site. Testing may occur for 12+ hours (p. 8) but no specific cutoff time was reported.

Upon arrival at the designated test site, individuals will be requested to complete a COVID-19 screening, then an overview of the testing logistics will be provided. Subjects will be instructed to wash a designated arm or leg (p. 27). They will then be provided a bug suit for protection. With the assistance of staff members, test subjects that are selected to be treated with repellent will roll up their bug suit sleeve or pant leg and an individual dose will be applied (solid stick or aerosol) and spread over the exposed treatment area by a staff member (p. 28).

Repellent-treated test subjects will be separated by a minimum of 10 feet apart and undergo 5-minute exposures at 30-minute intervals until CPT is achieved for each treated individual or until conclusion of the test day, whichever happens first. Four alternates will be available at each location at the start of the testing day to replace a test subject if they fail to show up or drop out before testing begins, or in the event too much of the test product is applied to a test subject. The alternate test subjects will be allowed to leave the testing site once the test substance has been applied to the treated test subjects (pp. 11-12). Subjects that withdraw once testing has begun will not be replaced.

Control test subjects will not be treated with any repellents and will monitor the mosquito pressure at the test site by exposing an untreated limb for 5 minutes at every 30-minute interval and counting the number of landings. Once 5 landings have occurred or the 5-minute time limit is reached the control test subject will cover the untreated, exposed portion of their limb. The target mosquito landing pressure will be a minimum average rate of 5 landings per 5-minute exposure period (p. 26). This landing pressure assessment will be repeated once approximately every 30 minutes "until all treated test subjects have experienced repellent breakdown, or the Study Director or Principal Investigator chooses to stop the test (p. 11)."

Sample Size and Number of Subjects

The protocol proposes 14 repellent-treated test subjects at each site for each product per day (28 treated test subjects total per site), two untreated controls per product at each site per day (4 untreated control subjects per site), and 4 alternates per product per site per day (8 alternate test subjects per site). This results in 20 individuals per product per site per day, or 80 individuals in total for the entire study covering both testing locations and both products.

Randomization

Test subjects will be identified by code numbers that will be assigned at the laboratory or field site training session. These codes will be used to randomly select 7 male and 7 female treated test subjects and 2 male and 2 female alternates per product. The Study Director will select untreated control subjects "*from subjects proficient at aspirating landing mosquitoes. This is to ensure that the subjects are well-versed in how to quickly recognize landing behavior and remove those mosquitoes before they bite*" (p. 26).

Study Plan

A pre-training day recruitment phase will employ several inclusion and exclusion criteria to identify qualified candidates who are representative of a typical insect repellent-using population from the general population of the United States. The selected candidates will be informed of the purpose of the study, the rules, and any potential associated health risks and will be required to sign an ICD upon arrival at their designated training session if they wish to proceed any further with the process. The laboratory or field site screening and training phase will include potential test subject consent and selection, attractiveness testing, aspirator training, and dosimetry for the solid stick picaridin product and will occur within 2 months of field efficacy trials.

The laboratory or field training is expected to take 2-3 hours (after the ICD is signed) and will start with attractiveness testing (unattractive subjects will not participate any further with the study), followed by aspirator training, limb measurements, and dosimetry testing for the picaridin solid stick product. Lab-based attractiveness training will use lab-reared adult females that have not taken a blood meal while field-based attractiveness testing will rely on wild mosquito populations (not lab-reared mosquitoes). However, individuals in the field training session will be wearing bug suits provided by study staff to prevent mosquito bites. Limb measurements will be taken, as described in the "Estimation of Skin Surface Area" section below, for the arms and legs of the test subjects so that the proper amount of product will be applied since test subjects' skin surface area will vary between individuals (pp. 23-24). A standard application rate of 1.0 g/600 cm^2 will be used for the 10% PMD aerosol product based on previous dosimetry testing for that active ingredient in an aerosol formulation while dosimetry testing will take place during the lab or field training session to determine the appropriate application rate for the 10% picaridin solid stick.

Field testing will take place at two ecologically distinct field sites where specific target species are found between the two test sites and the predominant mosquito species differ between sites. The field sites will be monitored weekly by local authorities to ensure no disease activity for at least one month prior to the field test day(s) and there will be communication

between researchers and the Norfolk County Mosquito Control District regarding mosquito-borne diseases (p. 17). The Study Director will utilize information provided on the United States Geological Survey (USGS), Centers for Disease Control and Prevention (CDC), and state health department websites to monitor any recorded occurrence of mosquito-borne diseases (pp. 20-21). If the necessary information is not readily available on those websites, then the Study Director will contact local health departments and mosquito control districts directly to acquire the data. Study staff will use CO_2 baited CDC miniature light traps at the WI testing site to collect and identify mosquitoes on a weekly basis the month before field efficacy testing is conducted (p. 17). Collection and identification at the MA testing site will be conducted by the Norfolk County Mosquito Control District using CO_2 baited CDC miniature light traps and the data will be shared with SC Johnson personnel.

Test Substance Application

A standard application rate of 1.0 g/600 cm^2 (based on previous dosimetry studies on file with the Agency) will be used for the PMD aerosol product. Dosimetry, described below, will be conducted to determine the application rate for the picaridin stick in the laboratory or field prior to field efficacy testing. For the field efficacy test, all test subjects will be instructed to wash a designated limb (forearm or lower leg) with unscented soap, dry it with a paper towel, and then wipe down the surface with a 70% isopropanol or ethanol solution and let it dry. They will then be given a bug suit and gloves and instructed to put them on. At a subsequent time designated by the Study Director (on the same day), each test subject will roll up their bug suit sleeve or pant leg and staff will use elastic bandages and surgical tape to hold the sleeve or pant leg in place immediately prior to application.

The solid stick picaridin product will be weighed and then swept over the treatment area on a test subject by a staff member until the appropriate amount is applied. The bandages and surgical tape will define the area of the limb that is treated on a test subject's exposed limb (p. 28). The stick will be weighed after initial application and more product will be applied if necessary to achieve the appropriate calculated amount (by weight) as determined by dosimetry. The aerosol product will be weighed and dispensed from a sample container onto a test subject's skin until the desired amount (by weight) is applied. A staff member will then spread the product using two fingers of a gloved hand to attain complete coverage over the application area. The glove used to spread the product will be weighed before and after application to see if and how much product was lost during the procedure (p. 28).

Dose Determination (Dosimetry)

Dosimetry testing will be conducted in the laboratory or at a designated field site prior to field efficacy evaluation of the picaridin solid stick to determine the appropriate test application rate to be used during efficacy testing. The test substance (solid stick in its dispensing apparatus) will be placed on a balance and measured before being provided to a test subject. The test subject will then be instructed to apply the repellent to their own limb as they normally would to achieve complete coverage before returning the test sample to a staff member (p. 27). A staff member will weigh the test sample post-application and record their measurement. The test subject will then wash the treated surface with unscented soap, rinse with water and dry with a paper towel,

and wipe down the limb with 70% isopropanol or ethanol. The test subject will then apply the repellent an additional two times (alternating treatment limbs) as instructed previously for a total of three individual applications. An average application rate (g/cm^2) will then be calculated from the three measurements to determine the final application rate to be used during efficacy testing in the field (p. 27).

Estimation of Skin Surface Area

Test subjects will have their non-dominant forearm and the opposite lower leg measured in the laboratory or field to determine the appropriate treatment surface area, which allows them to operate the aspirator with their dominant hand during testing (pp. 23-24). The forearm will be measured at the wrist just below the wrist bone, at the crease of the elbow, and at two points roughly equidistant between the wrist and elbow to establish the appropriate treatment surface area as follows:

Forearm surface area (cm^2) = C x D

C = Mean of the circumference measurements (in cm)
D = Distance between the wrist and the elbow circumference measurements (in cm)

The lower leg will be measured at the crease of the bent knee, immediately above the laterally protruding ankle bone, and at two points roughly equidistant between the knee and ankle to establish the appropriate treatment surface area as follows:

Lower leg surface area (cm^2) = C x D

C = Mean of the circumference measurements (in cm)
D = Distance between the knee and the ankle circumference measurements (in cm)

The treatment area for each test subject will be calculated using the forearm and/or lower leg surface area measurements as follows:

For the 10% picaridin stick:

Test substance (g) = Average application rate derived from the picaridin stick dosimetry determination multiplied by surface area of the test subject's treatment area.

For the 10% PMD aerosol:
Test substance (g) = 1.0 g/600 cm^2 multiplied by surface area of the test subject's treatment area.

Margin of Exposure

Field testing of two skin-applied repellents, one an aerosol product containing 10% PMD and the other a solid stick product containing 10% picaridin, will be conducted against wild populations of representative mosquito vectors. A standard dose of 1.0 g/600 cm^2 will be used for

the PMD product and dosimetry will be used to establish the appropriate application rate for the picaridin product.

PMD: A 90-Day dermal study in rats (MRID 44438710) tested PMD (98.3 % pure) at increasing doses, 0, 1,000 and 3,000 mg/kg/day. The No Adverse Effect Level (NOAEL) = 1,000 mg/kg/day, and the Lowest Adverse Effect Level (LOAEL) = 3,000 mg/kg/day. The endpoints for NOAEL and LOAEL are based on treated skin observations, erythema, edema, eschar, and histological observations in treated skin, increased acanthosis and inflammation at the highest dose of 3,000 mg/kg/day. No dermal absorption data are required for Tier I Toxicity data for registration of biochemical products. Therefore, without these data, dermal absorption is assumed to be 100%. Risk characterization for infants and children is based on data from one developmental study (MRID 44438711) in which the NOAEL = 3,000 mg/kg/day. No LOAEL was established, and thus, a 10-fold safety factor is applied for risk characterization. MOEs were not calculated because there are no endpoints of concern for the dermal route of exposure. The Agency concluded that there is reasonable certainty of no harm to populations or subpopulations (infants and children) from the use of PMD in insect repellent products applied to human skin.

Picaridin: The active ingredient picaridin is classified as toxicity category IV for Acute Oral (LD_{50} >5,000 mg/kg (MRIDs 51868905 and 44408748), Acute Dermal (LD_{50} >5,000 mg/kg (MRID 51868907 and 44408749), Acute Inhalation (LC_{50} > 4.364 mg/L (could be waived based on results from MRID 44408709), and Dermal Irritation (MRID 51868902). It is classified as toxicity category III for Eye Irritation (i.e., caused moderate eye irritation that cleared in 7 days or less; MRID 51868903) and is not a dermal sensitizer (MRIDs 51868906 and 44408752). MOEs were not calculated because there are no endpoints of concern for the dermal route of exposure. The entire chronic toxicity database was generated using dermal studies, including developmental/reproductive and chronic studies, and there were no systemic toxic effects identified that would be relevant to humans. In the acute dermal study, the LC_{50}, NOEL and NOAEL were all greater than 2,000 mg/kg, and there was no evidence of dermal irritation or dermal sensitization. The Agency concluded that there is reasonable certainty of no harm to populations or subpopulation (infants and children) from the use of picaridin in insect repellent products applied to human skin.

According to an EPA risk assessment for picaridin, "*Toxicity endpoints and points of departure were not selected for picaridin. A qualitative human health risk assessment was conducted in lieu of a quantitative assessment, due to the limited toxicity seen in the database. Although kidney effects were seen in rats in dermal and oral toxicity studies, the effects are a result of accumulation of alpha 2-u globulin (a_{2u}-g). Since a_{2u}-g is a male rat specific protein, kidney toxicity induced by its accumulation is not expected to occur in female rats, mice, or in any other species, including humans. Therefore, the kidney effects observed in male rats are not considered appropriate for use in human health risk assessment. Outside of the kidney effects, toxicity was limited to body weight changes seen only at the limit dose (1000 mg/kg/day); human exposure at this level is not anticipated in conjunction with the use of products containing picaridin in accordance with registered labels*." [3]

[3]Middleton, K., Figueroa, Z. Picaridin. Preliminary Human Health Risk Assessment in Support of Registration Review. December 5, 2014.

Stopping Rules

The protocol includes the following conditions for stopping field testing (p. 30):

- Inclement weather where test temperatures exceed 100°F or other unanticipated weather conditions arise that make it unsafe to remain outdoors (p. 30).
- Adverse reactions are observed during testing where the Study Director decides to remove the test subject immediately and instructs them on obtaining appropriate medical attention (p. 30).
- Safety reasons (p. 30).
- CPT is achieved by test subjects when the FCL occurs. Upon the FCL a test subject's participation for the day is complete (p. 29).

Withdrawal Criteria

Any potential test subject that is shown to be unattractive to mosquitoes based on the criteria outlined in the protocol will be prevented from participating in efficacy testing in the field (p. 9). Participants may withdraw from the study at any time without penalty or loss of benefits to which they may be otherwise entitled (p. 5). However, if they do choose to withdraw early, they will only be paid for the hours in which they have participated. The Study Director or Principal Investigator (PI) may ask any subject who does not follow instructions given in the ICD or by the study staff to withdraw from the study or end a particular subject's participation in the study "*at any time, and for any reason*" (p. 22).

Criteria for Data Use from Withdrawn Subjects and Replacing Subjects During Field Testing

No specific criteria were provided concerning data use from withdrawn subjects and replacing subjects during field testing.

Data Collection

All data collected on individual subjects is confidential. Reckner (for the Wisconsin testing) and Focus on Boston (for the Massachusetts testing) will collect data related to the general demographics of repellent users in North America to obtain a pool of candidates for the study. Data will be collected at each testing site by study staff that includes:

1. CPT for each treated test subject, which is the duration between test substance application and the FCL on a test subject's treated appendage.
2. Number of mosquito landings in five minutes or less of exposure for the untreated control subjects.
3. Number of mosquitoes captured by test subjects during field trials. Only mosquitoes that land on exposed skin of control and treated subjects will be collected and those landing on protective clothing of subjects will not be collected or counted.
4. Temperature, relative humidity, wind speed, wind direction, light intensity, and precipitation data will be collected by a weather station at each field site.

5. CO_2 baited CDC miniature light trap data (mosquito counts and identification) collected weekly over a month prior to efficacy testing in the field.
6. Mosquito-borne disease occurrences as reported on USGS and CDC websites, or comparable information from local state health departments and Mosquito Control Districts as necessary.

Data from both testing sites will be analyzed by an external statistician and stored by the SC Johnson Sensory and Claims Group.

Statistical Analysis

CPT data will be analyzed using the Kaplan-Meier Estimator for survival data analysis (p. 29). Additional statistical methods like arithmetic mean may be included if determined to be necessary based on the raw data.

How and to What Will Human Subjects be Exposed

During the field efficacy studies, test subjects will be exposed to a 10% picaridin solid stick or a 10% PMD aerosol formula. The aerosol product containing 10% PMD will be applied at a dose of 1.0 g product/600 cm^2 of skin to either a test subject's arm or lower leg. Dosimetry testing in a laboratory or at a field site will be performed for the solid stick picaridin formulation before any efficacy testing occurs in the field; the protocol notes that no test subjects will be allowed to treat themselves with more than 2.0 g product/600 cm^2 during the dose determination testing (p. 27). Field exposure time for each subject may be 12+ hours for a single day of testing. In the field, subjects will be exposed to natural mosquito populations relevant to public health where pathogens have not been detected at the test site for at least one month prior to testing. In the laboratory during pre-test attraction testing and aspirator training, participants will be exposed to lab-reared female mosquitoes that have not taken a blood meal. Subjects that attend pre-test attraction testing and training in the field will be wearing bug suits (hands will be protected with gloves and the feet with higher cut shoes or boots) and will be protected from mosquito bites from the surrounding wild mosquito population (p. 23).

Good Laboratory Practice (GLP) Compliance and Quality Assurance

Compliance with 40 CFR Part 160 (Good Laboratory Practice Standards) was reported as such: *"A final report will be issued by the Study Director and will include all the required elements to comply with 40CFR 160.185 and the most recent version of SOP GLP-RPT-01. The Quality Assurance Unit will inspect at least one phase to ensure the integrity of the study. In addition, the final report will be reviewed against the protocol, SOPs, and raw data for accuracy. A statement will be included in the report specifying inspection dates, phases, and the dates findings were reported to the Study Director and Management."*

Compliance with FIFRA and EPA regulations

Data resulting from execution of this protocol as well as study conduct will be reviewed

by the EPA for compliance with FIFRA 12(a)(2)(P) and 40 CFR 26 subparts K, L, and M, and will be independently audited by a QAU for compliance with Good Laboratory Practice Regulations (40 CFR 160). The QA representative will conduct critical phase inspections to ensure study integrity and maintain written and signed records of each inspection. The EPA will consult with the HSRB about the protocol and the EPA's review as required under 40 CFR 26.

Study Site Location and Testing Facility

Field Study Locations:

- Wisconsin site - Brighton Dale Links Golf Club, 830 248th Avenue, Kansasville, WI 53139
- Massachusetts Site - Hale Reservation, 80 Carby Street, Westwood, MA 02090
- Additional unnamed sites

Laboratory and Field Screening and Training Sites: No specific location information provided

Principal Investigator: Daniel Usry, S.C. Johnson & Son

Study Sponsor: S.C. Johnson & Son, Inc., 1525 Howe Street, Racine, WI 53403

C. Compliance with Applicable Scientific Standards

This protocol addresses the following elements according to applicable scientific standards:

- Test subject selection
- Experimental design
- Data analysis
- GLP compliance and quality assurance
- Risk minimization

D. EPA Science Comments and Recommendations

EPA recommends the study protocol should be revised as follows:

1. Picaridin stick references

   The Agency was initially asked to review a protocol that would be used for testing of a 10% PMD aerosol repellent (EPA registration number 4822PA51; DP 465257) and a 10% picaridin solid stick repellent (EPA registration number 4822PA52; DP 465253) against mosquitoes. The Agency was informed via email notification on 11/4/2022 that SC Johnson would no longer pursue the picaridin solid stick testing. The protocol was evaluated with both products in mind even though SC Johnson does not wish to pursue picaridin stick testing at this time.

2. Field site selection and composition

a. Add a field testing site that includes *Ae. albopictus* and/or *Ae. aegypti*. Absent testing with one of these species, the data generated would not be accepted to satisfy the requirement for efficacy data to register the product. The protocol's selected field sites and list of common species found at those sites (p. 17) do not include *Aedes aegypti* or *Aedes albopictus* as required under 40 CFR 158 for products making a claim against mosquitoes. Under this rule,[4] testing on the following genera and species is required:
    - *Anopheles* (*Anopheles albimanus* or *Anopheles freeborni* or *Anopheles gambiae* or *Anopheles hermsi* or *Anopheles punctipennis* or *Anopheles quadrimaculatus* or *Anopheles stephensi*); and
    - *Aedes* (*Aedes albopictus* or *Aedes aegypti*); and
    - *Culex* (*Culex pipiens* or *Culex quinquefasciatus* or *Culex tarsalis*).

The following link shows the potential geographic range for *Ae. albopictus* and *Ae. aegypti*: https://www.cdc.gov/mosquitoes/mosquito-control/professionals/range.html. Testing that includes the mosquito taxa specified above ensures that there are data supporting efficacy against the major disease vectors in these groups (e.g., *Ae. albopictus*/*Ae. aegypti* for Zika virus, etc.). Requiring data on major vectors is necessary to ensure that pesticide products are effective against species that may pose risks to public health.

b. Revise the protocol to include habitat description and the expected mosquito prevalence, and to make clear that the predominant mosquito species will differ between test sites. Repellency studies must be conducted in at least two distinct habitats as defined in the OPPTS 810.3700 Guideline, which could include forests, grasslands, salt marshes, wetlands, beaches, barns, or urban environments, where the predominant mosquito species differs between the sites, and the populations do not overlap between sites.

3. General study design

   The overall study design from initial ICD review and consent to attractiveness testing in the laboratory to product field testing needs to be revised. The following format is suggested: Recruitment and Informed Consent; Attractiveness Testing (in the laboratory); Aspirator Training (in the laboratory); Limb Measurements (in the laboratory); Dosimetry (in the laboratory); Field Site Monitoring; Field Testing.

4. Laboratory versus field training/testing

   The Agency recommends that Attractiveness Testing, Aspirator Training, Limb Measurements, and Dosimetry are only conducted in the laboratory and **NOT** in the field due to potential exposure to pathogen-infected wild mosquitoes. The laboratory also provides a more controlled setting where environmental conditions are consistent, the origin and status of lab-reared mosquitoes are known, and the use of bug suits is unnecessary. For example, there would be no need to expose potential test subjects to field conditions (including wild mosquitoes and potentially uncomfortable environmental

[4] https://www.federalregister.gov/documents/2022/04/15/2022-07963/pesticide-product-performance-data-requirements-for-products-claiming-efficacy-against-certain

conditions) if they are deemed unattractive to mosquitoes during laboratory-based attractiveness testing.

5. Attractiveness testing (field)

   The Agency recommends against conducting any portion of the Attractiveness Testing, Aspirator Training, Limb Measurements, and Dosimetry in the field due to potential exposure to pathogen-infected wild mosquitoes. The laboratory provides a more controlled setting where environmental conditions are consistent, the origin and status of lab-reared mosquitoes are known, and the use of bug suits is unnecessary. For example, there would be no need to expose potential test subjects to field conditions (including wild mosquitoes and potentially uncomfortable environmental conditions) if they are deemed unattractive to mosquitoes during laboratory-based attractiveness testing. Review the attractiveness testing criteria, OPPTS 810.3700 Guideline (Section (j), p. 26), and provide detailed justification if departing from the Guideline recommendations.

6. Attractiveness testing (laboratory)

   a. The Agency recommends that attractiveness testing be performed in only the laboratory and not in the field to greatly minimize the risk of exposure to pathogen-infected wild mosquitoes.
   b. Clarify if all individuals will be tested once or more than once for attractiveness. It is stated that subjects will get up to three attempts to demonstrate attractiveness, but not specifically stated that additional attempts will not be made once an individual is determined to be attractive (p. 23).
   c. The Agency requests that raw data from attractiveness testing, which includes number of attempts and time of landings, be recorded and reported in addition to the other data that will be collected from the study.
   d. Provide rationale for the mosquito density in the test cages during attractiveness testing (p. 9), which deviates from the OPPTS 810.3700 Guideline recommendation (Section (j), p. 25).
   e. Provide information on how mosquitoes used in lab-based testing will be certified pathogen-free. Mosquitoes not having been exposed to a human blood source (p. 12) does not necessarily assure they are pathogen-free. Molecular testing is typically performed to ensure pathogen-free status of lab-reared colonies.
   f. Specify in the protocol that the final report will include pertinent information about the mosquitoes used during attractiveness testing such as age, developmental stage, time of last blood meal (if relevant), and whether or not and for how long they were starved pre-testing. The OPPTS 810.3700 Guideline (Section (j), p. 27), suggests that test mosquitoes should be fed 10% sucrose but no blood meal before a test and starved for 12-24 hours immediately prior to testing.
   g. Revise the protocol to clarify that mosquitoes will be disposed of (and how they will be disposed of) after use with a subject and will not be used with more than one subject. The Agency recommends changing out the mosquitoes between attempts if a subject is not attractive.

7. Aspirator training (laboratory)

    a. The Agency recommends that aspirator training is performed in the laboratory and not in the field to greatly minimize the risk of exposure to pathogen-infected wild mosquitoes.
    b. Describe the specific criteria required to determine when test subjects are sufficiently proficient to aspirate mosquitoes after landings and participate in field tests. The language in the protocol is too vague and only says that individuals will be deemed proficient when a "*study staff member feels they are sufficiently proficient*" (p. 10). Determine a stopping point in the training where proficiency has been met based on replication of successful observation and capture of the test mosquitoes. It must be clear how many successful attempts are necessary and how many successful replicates are required until the participant is considered proficient. Indicate if there will be a cut off time limit for gauging proficiency.
    c. Mosquitoes used in aspirator training should be lab-reared, certified pathogen-free mosquitoes. Revise the protocol to indicate how the pathogen-free status will be confirmed and documented.
    d. Revise the protocol to clarify that mosquitoes will be disposed of after use with a subject and will not be used with more than one subject.

8. Limb measurements (laboratory)

    a. The Agency recommends that limb measurements are performed in the laboratory where individuals are not likely to encounter wild mosquitoes. They will also not be exposed to potentially uncomfortable or adverse weather conditions indoors.

9. Dosimetry (laboratory)

    a. The Agency does not recommend performing dosimetry at a field site. The Agency recommends conducting dosimetry in a laboratory setting, which provides a more controlled environment. Also, dosimetry cannot not immediately precede field testing since the time required for analyses of the doses derived from dosimetry and to calculate the test dose for the solid stick product would significantly impact testing time in the field.
    b. It is not explicitly stated how individuals that treat themselves during field-based dosimetry testing protect themselves from exposure to wild mosquitoes while will apply the picaridin stick to the surface of their limb (p. 27).
    c. The protocol indicates that a pavilion will be available for dose determination testing in the field (p. 27); confirm whether the pavilion will be fully enclosed and free of mosquitoes.
    d. Revise the protocol to include more specific information about dosimetry testing, including the number of subjects that are required to derive a typical consumer dose, and when the testing will be conducted in relation to the other training exercises that will take place on the same day. See the relevant sections of the OPPTS 810.3700 Guideline for additional guidance (Section (i), pp. 23-25).

e. Test subjects should be instructed to review the product label and apply the product, rather than being told to "*apply the test repellent to their own limb as they would normally apply a repellent to achieve complete coverage*" (p. 27).
f. Remove the statement that "*No test subject will be allowed to treat themselves with a greater than 2 g/600 cm^2 application rate*" (p. 27). This is not possible to achieve during an individual application. Additionally, it is inappropriate to limit application during the dosimetry phase where subjects are observed making their "typical" application.
g. After establishing a dose, SCJ needs to consult with the EPA prior to initiating field testing.

10. Efficacy testing (field sites)

a. Bug suits are not acceptable for insect repellent field testing due to heat stress and dehydration concerns. The Agency recommends a light-colored long-sleeved shirt, pants, and appropriate foot and head protection (i.e., closed-toe shoes, head net, and gloves) for field efficacy testing. The EPA determined in past decisions that Tyvek® suits made of high-density polyethylene fibers (plastic) were unacceptable when proposed for a similar purpose.[5]
b. Provide more specific information about an appropriate cut off time for the study, and whether the protocol's 12+ hours of testing start from the time of application, or at the time field testing begins. The study should be stopped if more than half of the test subjects experience CPT.
c. Revise the protocol to clarify precisely when untreated control and treated test subject observations will occur (pp. 28-29). The control subjects should establish landing pressure immediately preceding treated test subject exposure. Each exposure period will start with control subjects exposing their untreated limb first (5 minutes or 5 landings), immediately followed by test subjects exposing their treated limb for 5 minutes.
d. Revise the protocol discussion around minimum mosquito landing rate. The Agency's criteria have been at least 5 landings within 5 minutes on each of the control subjects, not an average of 5 landings over multiple time points. Remove from the protocol the minimum average landing rate of 5 lands over 5 minutes (p. 26).
e. The Agency recommends supplying a proposed efficacy testing schedule, as a chart or informative graphic (or both), to clarify several important factors including the location, time of day testing is expected to occur, and which specific product(s) will be tested on each test day.

11. Field site monitoring

a. Selected field sites need to be monitored and certified free from mosquito-borne pathogens for at least one month within 25 miles of the test site prior to any test

[5]Fuentes, C., Hull-Sanders, H., Arling, M. Science and Ethics Review of a Protocol for Field Evaluation of Two Topically-Applied Insect Repellent Products Containing IR3535. https://www.epa.gov/sites/default/files/2021-01/documents/a._livful_ir3535_protocol_science_and_ethics_review_2020_12_18.pdf

subjects being present for field training and/or field efficacy testing. Please note that the Agency does not recommend field training sessions as previously stated.

b. The protocol should include additional details about mosquito monitoring at the test sites including what type of (including manufacturer) and number of traps that will be used, trap locations, mosquito species targeted, when traps will be active, and intended frequency of specimen collection. The protocol should indicate that the final report will contain these trapping details as well. The Agency also recommends that you provide copies of raw data sheets showing what information will be collected and what information will be reported.
c. The Agency recommends that monitoring at each test site follows EPA Guideline OPPTS 810.3700, Section (k) (pp. 29-31) and the details are precisely communicated in the protocol for each site. Monitoring should include identifying any collected specimens to genus and species, and screening collected mosquitoes for pathogens.
d. CO_2 baited CDC miniature light traps are not the most efficient tool for monitoring *Aedes* mosquitoes (particularly *Ae. albopictus* and *Ae. aegypti*) and could underestimate their population in the testing area. The Agency recommends pairing CO_2 baited CDC miniature light traps and BG-Sentinel traps for a more accurate estimate and including device-specific parameter details like the amount of CO_2 that is released and whether a lure is present in the device description.

12. Test substance application

a. Revise the protocol to provide more and consistent detail when describing how the test substance will be applied, including specifying whether a staff member is making the application or a test subject, how many staff members will be involved in test product application, what specific device will be used for application, when and if staff will assist with application, how researchers will ensure that the proper amount of product is dispensed, and what precautions will be implemented to ensure the test substance is not disrupted after it is applied to a test subject.
b. The researchers must ensure that the test substance is applied almost simultaneously to all test subjects to minimize deviations. Please describe what procedure will be followed to ensure consistency across applications.
c. Provide a detailed description of the procedure for measuring the amount of aerosol spray applied to each subject (i.e., weight of the can before and after dispensing, type of balance used for weighing the product and the calibration of the balance, how to apply the correct amount to a test subject). Include the specific gravity of the spray product as it will be used to convert weight (grams) to volume (mL) utilizing the following formula:

$$Dosage\ \left(\frac{mL}{cm^2\ of\ skin}\right) = \left[\frac{X\ grams}{600\ cm^2\ of\ skin}\right]\ x\ \left[\frac{1\ mL\ product}{specific\ gravity\ (g)}\right]$$

13. Randomization

a. Revise the randomization process (pp. 9-11) to include more precise details. Additional information should describe when the code numbers will be assigned to

test subjects and what method will be used to choose the code numbers at random when assigning individuals to the treated, untreated control, and alternates group (e.g., whether they be computationally assigned, drawn from a hat, etc.).

b. Control subjects should be selected randomly, rather than "*selected by the Study Director from subjects proficient at aspirating landing mosquitoes*" (p. 26).
c. Clarify whether the same subjects will be allowed to participate in more than one day of testing.
d. Describe how subjects will be assigned randomly to field sites and if any aspect of the study will be blinded. Specific details must be provided on how subjects are assigned to a product and sites (or test days).

14. Statistical analysis

The Agency recommends replacing the text under "Statistics" on page 29 of the protocol with the following: "CPT data will be analyzed using the Kaplan-Meier Estimator for survival data analysis, and the medians CPT (mCPT) and their 95% CIs (where log-log transformation is applied to survival function to obtain the confidence interval) will be estimated and presented along with figures of Kaplan-Meier survival curves." The log-log transformation should be used to calculate the 95% CI since the sample size of this study was obtained from simulations of power vs. sample size where the log-log transformation was used to calculate the 95% CI.

15. Withdrawn test subject data

Provide more information about how data from test subjects that withdraw from the study will be handled. Specific criteria must be provided describing how data from subjects who withdraw a few hours into testing will be treated for statistical analyses. If such subjects are not replaced, their data should be treated as right censored. If they were to be replaced, then criteria must be established on when to replace, that is, how far into testing a subject can or cannot be replaced and their data be used or discarded. The Agency does not typically accept replacement of subjects in a repellency field trial after the test substance has been applied to all test subjects, so a detailed justification would need to be provided to support an argument suggesting otherwise.

16. Stopping rules

The Agency recommends adding to the stopping conditions of the protocol to include mosquito landing pressure falling below acceptable levels (p. 30). Specifically, testing should cease if more than 15% of the total number of projected exposure periods have less than 5 landings within 5 minutes on either of the untreated controls, and no more than 15% of all exposures may be skipped or missed due to inclement weather. It may also be prudent to include specific "bad weather" conditions in the stop rules that may compromise the test results (i.e., rain that results in fewer mosquitoes out foraging).

17. WHO reference

The EPA recommends removing any references to the WHO publication *Guidelines for Efficacy Testing of Mosquito Repellents for Human Skin*[6]. The Kaplan-Meier calculation presented in Annex 3 (Estimation of Median and Confidence Interval of Complete Protection Time Using the Kaplan-Meier Survivor Function) of this 2009 WHO publication is incorrect. In particular, it appears that WHO misinterpreted a formula[7] and therefore used incorrect values in the calculation which resulted in the wrong answer in the WHO example.

18. Data collection and reporting

    a. The Agency recommends inclusion of a sample data collection sheet as part of the protocol. The data collection sheet should show how and what type of information will be recorded at each test site. The data sheet should include, but is not limited to, the time of product application to each test subject, calculated amount of product applied per test subject, actual amount applied per test subject (taking into account percentage of product lost to gloves during application, i.e., difference in weight of gloves before and after application), time of initiation of each exposure period, time of each landing, and total time (in minutes and hours: minutes) to FCL. For untreated controls, the total number of mosquitoes that landed on each control subject in 5 minutes or less as well as the time of each landing should be reported.
    b. Clarify how the data will be collected, including who will be performing the recording, whether treated test subjects will be working in pairs with other test subjects, whether control subjects will be paired with each other or with a researcher, and how collected mosquitoes will be stored (labeled vials marked with identifying information like date, site, time of collection, subject ID number, etc.) and transported to the laboratory for identification.

19. Final report

    Refer to the OPPTS 810.3700 Guideline (Section (g), pp. 23-24) when drafting a final study report, and ensure that the report includes details specified in the Guideline as well as the required elements established under 40 CFR 160.185. The final report submission must also be accompanied by the information required under 40 CFR 26.1303.

E. Summary Assessment of Ethical Aspects of the Proposed Research

Here is a summary of the EPA's observations about the ethical aspects of the proposed research. Attachment 1 provides supporting details and a point-by-point evaluation of this protocol.

1. **Societal Value of Proposed Research:** This study is designed to determine the efficacy of two topically-applied mosquito repellents (10% Icaridin Stick and 10% PMD Aerosol) through testing the product against mosquitoes in the field using human subjects. As intended, the data resulting from this proposed study will be used to support registration

[6]Link at: http://whqlibdoc.who.int/hq/2009/WHO_HTM_NTD_WHOPES_2009.4_eng.pdf
[7]More specifically, it seems that they selected the wrong "n" to use

of the two products being tested. Efficacy at preventing mosquitoes from landing on each subject will be expressed as CPT, which is defined as the time between application of the repellent product and the occurrence of the first mosquito landing on the treated skin followed by a second landing within 30 minutes. These data will be combined and analyzed to determine a median CPT (mCPT), which will be used to develop product labeling. The research has societal value because people are at risk of contracting mosquito-borne diseases, and such risks can be mitigated by the use of insect repellent products.

In addition, the protocol calls for establishing a typical consumer dose for the stick product containing picaridin. These data are necessary as there have not been studies to establish standard dosing for this type of product, and a standard dose is necessary in order to conduct field testing. The typical consumer dose derived from the dosimetry phase of the study will be used as the dose for the picaridin stick product during the field testing of the product's efficacy.

2. **Subject Selection:** The protocol calls for testing each product with 14 test subjects, with an equal number of males and females (p. 3). There are discrepancies between the protocol and consent form, where the consent form notes that only 12 treated subjects will be needed for each test day (p. 8). An additional two individuals will participate in the testing as untreated controls, monitoring mosquito landing pressure immediately prior to each exposure period. For each product tested, subjects will be randomly assigned to serve as a test subject or untreated control based on their order of arrival on the test day. In addition, five subjects will be enrolled as alternates to take the place of any test subjects who withdraw before or on the day of testing (at least two subjects of each gender). A total of 20 individuals (14 test subjects, 2 untreated controls, and 4 alternates) will be selected to test each product. Therefore, a total of 40 subjects would be needed assuming each individual participates only in a single test day. The protocol calls for recruiting 30-40 individuals per test site, for a total of 60-80 individuals recruited.

   The protocol calls for recruiting a diverse pool of candidates. The pool will be balanced by gender. Ages will range from 18-55 years old, with approximately 20%-40% in the 18-30 range, 30%-50% in the 31-44 range, and 30%-50% in the 45-55 range (p. 3). Racially, the goal is to recruit a pool including individuals identifying as: Caucasian (50%-85%), African American, Asian, or other (5%-25%), and Hispanic (5%-25%) (p. 3).

   Subjects will be recruited from the area local to the test sites (Kansasville, Wisconsin and Boston, Massachusetts) by an independent recruitment agency at each site (Reckner in Wisconsin, Focus on Boston in Massachusetts) (pp. 4 and 18). The protocol includes demographic targets for recruitment (p. 18). Enrollment will be limited to English-speaking individuals (p. 18). In addition, subjects must not be employees of SC Johnson or immediate family members of SC Johnson,

   The recruitment materials provided with the protocol indicate that first contact with potential subjects will be made by the recruitment firm (Procedure for Initial Contact in Recruiting Test Subjects via email for Insect Repellent Bio-Efficacy Studies). This

contact script describes the purpose of the study; the procedures that will be used for training, attractiveness testing, and efficacy testing; compensation for subjects; and eligibility criteria. The end of this document that would be emailed invites candidates who self-identify as meeting the criteria to review the informed consent form, to ask questions if they have any, and to sign the informed consent form if they are interested in participating (Procedure for Initial Contact in Recruiting Test Subjects via email for Insect Repellent Bio-Efficacy Studies, p. 3). The protocol notes that individuals who are interested in participating in the study and who meet the necessary criteria would be invited to attend a test subject training session lead by study staff members (pp. 17-18).

Prior to field testing, subjects will participate in a mosquito attractiveness test and training on how to use an aspirator. There are two proposed methods to verify attractiveness to mosquitoes – in the lab using mosquitoes in a cage, in the field using wild mosquitoes (p. 23). In the lab, testing would involve placing an untreated forearm into a cage measuring 2'x 2' x 2' and containing 50 adult, female mosquitoes. Subjects will be considered attractive if they have 5 mosquito landings on their arm within 1 minute. In the field attractiveness testing would involve subjects wearing a full bug suit, exposing a forearm or lower leg, and counting mosquito landings. In the field, an individual would be deemed attractive if they have five mosquito landings on the untreated skin within 5 minutes. The protocol notes that subjects will have three chances to demonstrate attractiveness to mosquitoes, but if they do not acquire at least five landings in the prescribed period, they will be deemed unattractive and ineligible to continue in the study.

The protocol also notes that "*subjects will be taught to use a battery-powered aspirator and will practice using the aspirator to collect landing mosquitoes until they and the study staff feels* [sic] *they are sufficiently proficient to participate in the field test*" (p. 23).

On each day subjects are exposed to the test substance or mosquitoes, female subjects will be required to take a pregnancy test to confirm their eligibility to participate in the research (p. 4). This test will be administered by the subject alone in a private bathroom at the start of the test day. A female member of the study staff will discuss the results of the pregnancy test with the subject in a private setting. If the subject is interested in continuing to participate in the study, the female staff member will verify the negative test result privately (p. 4).

Subjects will also be required to adhere to pre-testing restrictions in order to participate in the testing. Subjects will be instructed not to drink alcohol for the 12 hours prior to the test, and to refrain from smoking, chewing tobacco, and using fragrance products during the test day (p. 12).

3. **Risks to Subjects:** The protocol discusses potential hazards associated with these tests including: 1) adverse reaction to the test substances, 2) exposure to biting mosquitoes, 3) exposure to mosquito-vectored diseases, 4) general risks of being in the field, 5) risk of exposure to Covid-19, and 6) unanticipated loss of confidentiality.

The protocol notes that risks will be minimized as follows. To mitigate risk of adverse reaction to the test substances, safety data sheets will provide evidence of low risk when used as directed (p. 20). The dose for the picaridin stick product will be established by consumer dose testing, and the protocol calls for ensuring that the dose is no more than 2 grams/600 cm^2 (p. 17). During the dosimetry testing, individuals will make the application and immediately wash the limb to which the application was made. Following the three applications during the dosimetry phase, subjects will have washed each of the limbs to which applications were made to remove the product applied. To mitigate the risk of exposure to biting mosquitoes, individuals with known allergies to mosquito bites will be excluded, subjects will be trained on aspirating mosquitoes before they bite, and subjects will only expose one forearm or lower leg periodically (p. 20).

To minimize the risk of contracting any mosquito-borne diseases, the protocol notes that subjects will be informed about the symptoms of mosquito-borne illnesses and instructed to seek medical care in the event they experience symptoms (p. 20). Additionally, testing will only be conducted in areas where there has been no detected presence of mosquito-borne disease by a county or state agency or mosquito abatement district within a month of testing (p. 20). The Study Director will consult various resources (Centers for Disease Control and Prevention, state health department websites, mosquito control districts) to obtain this information if it is not available on the internet (pp. 20-21). Finally, subjects will be trained to use an aspirator to remove mosquitoes from their skin before the mosquitoes bite (p. 21).

General risks of being in the field include risks of exposure to wildlife and other biting insects, risk of injury due to rough terrain, and physical stress associated with being outdoors for over 12 hours in a hot and humid environment. These will be mitigated through study staff providing food and beverages to keep the subjects hydrated and comfortable, having a pavilion at the test site to provide subjects with shade between exposure periods, avoiding wildlife, encouraging subjects to perform tick checks and to remove ticks as soon as they are identified, providing first aid assistance to subjects at the field during the test day, providing standard first aid items (bandages, antiseptics, antihistamines), and reminding subjects to inform the study staff at any time if they feel unwell (p. 21). Study staff will identify the closest hospital to each test site and will be prepared to accompany a subject who requires medical attention.

The study staff will follow local and state health and safety guidelines to mitigate the risks of Covid-19. For all in-person encounters, subjects will review a set of screening questions and have their temperature checked prior to continuing with testing-related procedures (p. 21).

The risk of unanticipated loss of confidentiality will be mitigated through protecting all individuals' personal information. Subjects will be assigned a code number, which will be used to identify them on all study-related data sheets. The report will be kept confidential, and if any results are published the subjects' identities will remain confidential. Study records will be maintained in locked cabinets, electronic files will be kept on a password-protected server, and access to personal information will be limited to

SC Johnson, the study staff, the recruitment firm, the IRB, and the US EPA (p. 22).

Additional risks to subjects include the psychological risks associated with pregnancy testing and the risk of contracting mosquito-borne diseases during lab-based testing procedures. Pregnancy testing will be conducted in private and only a single female member of the research team will discuss the results with the subject.

Practical steps to minimize most subject risks have been described in the protocol. With the comments from the EPA addressed, risks to subjects will be effectively minimized and the remaining risks will have a low probability of occurrence.

4. **Benefits:** This research offers no benefits to subjects. Depending on the results of the research, it may benefit society by generating reliable repellency efficacy data that could be used by the EPA to register insect repellent products containing the ingredients tested. Registration of effective repellent products could lead to fewer mosquito bites and reduced incidents of vector-borne illnesses. The Study Sponsor could benefit financially from the registration of these products and their eventual marketing and sale.

5. **Risk/Benefit Balance:** The protocol describes a procedure for generating scientifically sound data and includes measures to limit the risks to subjects participating in the study. With the risk mitigation measures put in place and provided that the EPA's comments are addressed, the remaining risk to subjects is low and reasonable in light of the potential benefits of the data to society.

6. **Independent Ethics Review:** The Western Institutional Review Board (WGC IRB) has reviewed and approved the protocol, informed consent form, and recruitment materials. On March 3, 2022 the protocol and materials were conditionally approved provided that changes to the consent forms were made. On March 8, 2022, a Certificate of Action dated indicated that WCG IRB had approved the protocol, consent forms, and recruitment script. The WGC IRB is registered with the Office of Human Research Protections (IRB00000533) and is accredited by the Association for the Accreditation of Human Research Protection Programs. Satisfactory documentation of the IRB procedures and membership is on file with the Agency. Documentation regarding IRB approval of the protocol, consent and recruitment materials has been provided to the HSRB members with the background materials for this review.

7. **Informed Consent:** The protocol calls for having the independent recruitment agency send the consent form to interested candidates by email (p. 4). The consent form notes that subjects will be scheduled for a training session, at which they will review the consent documents, have the study staff review the form with them, and have an opportunity to ask questions before deciding to consent to participate (p. 9).

   The recruitment script notes that "*If you meet the criteria to participate, please review the attached Informed Consent Form. If you have any questions on the research or have questions to be answered before you sign the informed consent form, please contact [ENTER RECRUITMENT FIRM CONTACT NAME]. We will be sure to have all your*

questions addressed before you sign the consent form. If you do not have any questions and are interested in volunteering please complete the informed consent form." (Recruitment Script for Boston, p. 3)

In all instances, the consent process informs individuals that their participation is voluntary and that they can withdraw from participation at any time without forfeiting benefits or compensation.

The protocol does not specify what the consent meeting/training session will cover, whether it will be held as a one-to-one or group session, whether there will be demonstrations of all study-related procedures as part of the consent process, and how potential subjects' comprehension of the study's procedures will be gauged before they are invited to complete the informed consent document.

8. **Respect for Subjects**: The subjects' identities will be protected as follows: each subject will be assigned a code number/identifier. The study records will be maintained in locked cabinets, and electronic files kept on a password-protected computer server or encrypted electronic storage devices. Provision is made for discrete conduct of the pregnancy testing that is required of female subjects on the day of testing.

   Throughout the recruitment and consent processes, and again at the start of each test day, candidates and subjects will be informed that they are free to decline to participate or to withdraw at any time for any reason.

   The protocol notes that subjects will be compensated for their time spent participating in the study as follows: $100 for the participating in the training meeting and $35 per hour (rounded up to the next hour) for participation in a test day. If the test day is postponed due to weather, subjects who were available for the test day will be compensated $60 for being available and will be invited to participate on the rescheduled test day. Alternates who are asked to show up at the test site will be paid $100 for their time (p. 13). Subjects who participate in the dose determination study will be compensated $100 for their participation in session, which is expected to last 2 hours (p. 22). The amount of compensation seems reasonable in light of the inconvenience of being in a field and subject to mosquitoes and hot, humid conditions for 12+ hours. The amount of compensation does not seem sufficiently high as to unduly impact a subjects' decision to participate in the research.

   Breaks for subjects between exposures and provision of snacks and drinks have been incorporated into the study design.

   Any expenses for injury or illness incurred as a result of study participation will be paid by the study sponsor (p. 13).

F. Compliance with Applicable Ethical Standards

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to the EPA under the pesticide laws. The primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply. A point-by-point evaluation of how this protocol compares with the requirements of 40 CFR 26 Subparts K and L and the criteria recommended by the HSRB is appended as Attachment 1. As noted below and in Attachment 1, revisions are needed in order to generate research that is likely to meet the standards of 40 CFR 26, Subparts K and L.

With the EPA's comments on the consent form and protocol addressed, the consent materials and process will meet the requirements of 40 CFR 26.1116 and 26.1117. With the protocol and all associated materials revised according to recommendations from the EPA and the HSRB and approved by the WGC IRB, the research will likely meet the applicable requirements of 40 CFR part 26, Subparts K and L. The materials to be used to recruit subjects (advertisements, scripts) must be provided to the EPA prior to the initiation of the study in order to comply with the requirements of 40 CFR 26.1125.

G. Ethics Comments and Recommendations

The EPA's ethics comments are provided below. Minor comments on typographical errors have not been included here. In addition, the EPA has provided ethics-related comments directly on the screening scripts to be used during recruitment; these are provided to the HSRB as a separate file. After all necessary changes have been made, the revised protocol and supporting documents must be resubmitted for review and approval to the overseeing IRB prior to initiating the research.

1. On page 1, revise the first statement as follows: "*This study **IS** ~~NOT~~ intended for submission to US EPA in support of a registration*."

2. Revise the document to be a single protocol outlining how the study will be conducted from start to finish. A researcher unfamiliar with the study should be able to pick up the document and understand how to carry out the research. The informed consent, statistical support for sample size, advertising materials, recruitment scripts, and any other study-related support materials should be included as appendices to the protocol document. See the science review recommendations for a suggested organization.

3. Sample size – The EPA recommends a sample size of 13 based on an EPA-conducted power analysis. The inclusion of an additional subject is unnecessary to ensure an adequate sample size for statistical analysis and unnecessary exposure of subjects is unethical.

4. Stopping rule – Include an additional stopping rule indicating that testing will be stopped when 7 subjects (over half) experience FCL. At that point, the mCPT can be calculated and further exposure of human subjects is unnecessary and therefore unethical.

5. Bug suits – The EPA recommends against the use of bug suits. Site monitoring, capturing mosquitoes that land on subjects, training the subjects on aspirator use to catch mosquitoes before they bite, and providing a screened enclosure for subjects to use between exposure periods effectively minimize the risk of contracting mosquito-borne illnesses. The use of bug suits presents additional, unnecessary risks of heat exhaustion and heat stroke.

6. The EPA recommends against having the consent meeting and the subject training session (attractiveness testing and aspirator use) conducted concurrently or sequentially on the same day. Separating these into two distinct interactions with the study team would reduce the pressure for subjects to enroll and would give subjects adequate time to consider whether they want to participate after going through the consent process with the Study Director. It is possible to hold virtual consent sessions and to have individuals sign the form electronically or in person when they participate in the in-person training session. Subjects should not participate in any aspect of the testing prior to giving fully voluntary, informed consent.

7. Eligibility criteria
    a. Employees and family members of any entity involved in the study (e.g., recruitment firm, contract research organization) should also be excluded from participation.
    b. Clarify whether SCJ will provide unscented soap for subjects to use and whether subjects may use fragrance products immediately prior to their participation in the test (p. 3).
    c. Confirm whether subjects will be permitted to participate to test both repellents and to test at both sites, or whether subjects are limited to testing a single repellent at a single site.
    d. Although the EPA's guidelines recommend that subjects are between 18 and 55, feedback from the HSRB and discussions of previous protocols have changed the recommendation to remove upper age limit or provide rationale for excluding subjects over 55 years old. Please revise the protocol to address.
    e. Specify the specific health conditions that would make individuals ineligible to participate and/or how information will be obtained from the potential subjects and evaluated by the Study Director.
    f. The eligibility criteria limit the participation of subjects to English speakers. The research does not offer benefits to subjects so lack of access to the research does not deprive non-English speakers of any benefits from participation. The research is also generalizable to the US population regardless of the language spoken by the subjects. However, enrolling non-English speakers would make the study enrollment more equitable and should be considered by the researchers.

8. Pregnancy testing – Ensure that throughout the protocol and consent form it is clear that female subjects will be subject to pregnancy testing prior to any exposure to mosquitoes or the test substance (p. 20), rather than only on the test days (pp. 4, 8).

9. Recruitment

a. Recruitment should not be initiated until after the protocol has been reviewed by the EPA and the HSRB, any recommendations have been addressed, and the final version has been approved by the WCG IRB.
b. Provide more specific details in the protocol on how recruitment will be conducted using the recruitment firms. How will recruitment firms identify individuals who might be willing to participate in the study? Will advertisements be posted to which people can respond? Will the subjects be drawn from a pool of individuals who have expressed open willingness to be contacted about participating in the study?
c. Clarify in the protocol how email will be employed in the recruitment process. What advertisement will be emailed and to whom will it be emailed? How will the distribution list be established?
d. Include in the protocol measures that will be taken to ensure that subject selection is equitable.
e. Amend protocol to note the total number of subjects that will be recruited for participation to ensure that a representative sample (age, gender, race/ethnicity) can be selected for the field testing on each day. If the protocol calls for 20 subjects per test (15 test/control subjects, 5 alternates), consider how many additional subjects should be recruited and screened to ensure that there is a sufficiently large pool to choose from. It is reasonable to have for each test day/site, a pool of potentially eligible participants that is double the total number of subjects needed for that test day/site, e.g., a pool of 40 subjects to fill the 20 slots needed for testing the PMD product in Wisconsin.
f. All recruitment materials, including advertisements, must be provided to EPA and approved by the IRB prior to use.

10. Informed consent document and process
    a. Remove the consent form from the body of the protocol and include as an attachment to the protocol.
    b. Expand the discussion of the consent process in the protocol. It should include more specific details about what will be covered (the entirety of the consent form rather than the inclusion/exclusion criteria), as well as whether it will be a one-on-one or group session, whether individuals will be able to ask questions of the Study Director in private, and where it will be conducted.
    c. The consent process should include a demonstration of all of the procedures that will be used in the study, including attractiveness testing, aspirator use training, dosimetry testing, product application, and an exposure period on the test day.
    d. Individuals should be given time to consider whether they want to participate before being required to provide consent.
    e. Before inviting subjects to sign the consent form, the Study Director or person conducting the consent meeting should ensure that the subject has understood the materials provided in writing, presented, and demonstrated. Include the method by which potential subjects' comprehension will be evaluated in the protocol.
    f. The consent form must be revised to include all relevant elements of consent required under 40 CFR 26, Subpart K, including the simple summary of the study and the identity of the test substances.

g. The consent form and discussion must identify the test substance(s). Information such as the SDS should be available to subjects.
h. Delete the statement that "If you have a serious reaction to the product, you will be told what ingredients are in it." (p. 12) All subjects will be informed of the active ingredients in the test products. Any subject who experiences any reaction to the test substance may need be informed of all of the products' ingredients if necessary to provide medical treatment.
i. Add a statement that evaluating adverse effects may require the study personnel to consult with the treating medical personnel, after obtaining the subject's consent. For example: "The Sponsor, medical monitor, and the Study Director will determine whether the injury is related to the subject's participation in this study. To do this, they may request to consult with the person/facility that provided medical treatment following an adverse effect, which could require your consent."
j. The consent form should be revised to align with all changes made to the protocol and to address all of the EPA's specific comments on the consent form.
k. Clarify what "five individual tests" will be carried out during the study, and whether subjects can participate in more than one day.
l. Revise the consent form to reflect the correct number of subjects in the study.
m. Indicate whether the data from subjects who withdraw will be included in the study results, and if so, under what conditions.
n. All subjects should receive a copy of signed consent form (printed or electronic), without requesting it from the recruitment firm (p. 14).
o. The consent form should include one of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

    (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject, if this might be a possibility; or

    (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

11. Attractiveness testing and training on aspirator use
    a. Regarding mosquitoes used in the attractiveness testing and aspirator training, please clarify whether the mosquitoes will be destroyed after use in each test or whether mosquitoes will be reused in either the attractiveness testing or aspirator use training.
    b. Specify in the protocol how the disease-free status of mosquitoes used in lab-based testing will be confirmed/documented.
    c. Will subjects who make more than one attempt during the attractiveness testing use the same batch of mosquitoes or a new batch?

12. Risks to subjects – This section should be revised to appropriately identify all risks and to indicate how known risks to subjects will be minimized.
    a. Risks of exposure to the test substance will be minimized by excluding subjects with skin conditions that could be exacerbated by exposure to the test substance and subjects with known allergies to insect repellent products.
    b. Exposure to biting mosquitoes should be minimized by having subjects wear appropriate gear, such as hat with head net, gloves, long-sleeved shirt, pants, and closed-toed shoes or boots. As noted in the science review and the recommendation sections about the eligibility criteria, the EPA recommends against the use of bug suits, which are similar to Tyvek suits, in field testing due to the significant risks of heat-related illness when worn for long periods in hot, humid environments. Further, this risk can be mitigated by conducting all non-field testing study procedures (training, attractiveness testing, dosimetry) in a lab setting.
    c. In addition to coordination with the state and local public health districts and mosquito abatement districts, risks to subjects should be minimized through trapping at the test site for at least one month prior to the field testing, and testing collected mosquitoes to identify any diseases.
    d. The pavilion provided at the test site should be fully screened to keep mosquitoes and other insects out. Seating should be provided for subjects to rest between exposure periods to minimize the risk of exhaustion.
    e. Exposure to biting mosquitoes in the lab during aspirator training and testing should be mitigated through the use of batches mosquitoes from a lab-reared colony that have been certified as pathogen-free. The pathogen-free certification should indicate the specific diseases for which the mosquitoes in the batch/colony were screened and when the screening occurred.
    f. Consider including the risks of heat-related illness specifically, and including in the consent form and/or in the discussion at the beginning of each test day information for subjects about how to identify symptoms of heat-related illnesses.
    g. Specify who will provide "qualified first aid assistance" to the subjects during the field testing and what the qualifications are.

13. Include a specific section in the protocol on how adverse events will be identified, evaluated, and reported to the IRB. This should explain who will be determine whether adverse events are related to participation in the study and whether they are serious, and the qualifications of the person or team making the determinations.

14. The protocol should include language about the Sponsor's agreement to pay for any medical expenses associated with treating a study-related illness or injury.

15. The protocol should indicate whether the study will have a medical monitor, and the specific role the medical monitor will play during each test day. Additionally, if any medical personnel (e.g., doctor, nurse, emergency medical technician, certified first aider) will be present for each test day, specific the person, their qualifications, and role at the test site.

16. Compensation
    a. Indicate whether individuals will be compensated for participating in a consent meeting regardless of whether they enroll, and if so, how much.
    b. Specify whether subjects when subjects will be compensated, e.g., at the end of their participation or at the end of each interaction with the study team.
    c. The recruitment forms specify a difference in compensation for alternate subjects; one indicates that subjects would receive $50 for being an alternate and the other indicates that subjects would receive $100 for being an alternate. Revise to be consistent with the protocol, which indicates all alternates who are not enrolled as test subjects will receive $100.

17. Dosimetry
    a. The protocol calls for establishing a typical consumer dose for the picaridin stick product through dosimetry testing in a laboratory or at a field site prior to conducting any field efficacy testing is performed. Dosimetry is ethically justified for the picaridin product because no standard dose for field testing has been established, and such a dose can be established through the observation of human subjects making typical applications to their own skin.
    b. The protocol also notes that test subjects would not be allowed to treat themselves with more than 2.0 g product/600 cm^2 during dose determination testing. Limiting the dose applied during the dose determination phase is impractical and unethical, because it would not accurately reflect the amount of product typically applied by consumers using the product and would bias the resulting dose calculated for use in field testing.
    c. If dosimetry testing for the picaridin product is pursued, the protocol should be revised to indicate a statistically-supported sample size for conducting a dosimetry test. If data are not scientifically valid, then it is not ethical to rely on the data. Additionally, SCJ should consult with EPA prior to using the dose derived through dosimetry to confirm that it is an appropriate level for field testing.

18. Field site selection and monitoring
    a. Prior to field testing, consistent mosquito landing pressure for the proposed duration of testing should be confirmed in order to avoid engaging subjects in testing and applying repellents unnecessarily. The protocol calls for basing the site selection weekly testing conducted by SCJ and the Norfolk County Mosquito Control District (p. 17); this should be revised in accordance with the EPA's science comments. Trapping before testing occurs ensures that there are diverse mosquito species and screening for diseases prevents testing where a known vector-borne illness has been identified. Consistent adequate landing pressure allows a test day to proceed to completion, thereby minimizing human exposure to both the test substance and mosquitoes to the greatest extent possible.
    b. Revise the protocol to include screening the mosquitoes captured at the test site for pathogens that could be carried by the species present in order to increase the likelihood of identifying any mosquito-borne diseases present at the test site and

to further minimize the risk of subjects being exposed to mosquito-borne diseases during the field testing.

c. Identify all potential test locations in the protocol and explain how site monitoring will be conducted at each of the sites. The addition of any site not listed in the protocol will require an amendment to the protocol submitted to and approved by the IRB before any work at the site can begin. The amendment should provide in detail the information about how the site will be monitored prior to the field testing day(s), the process for trapping and screening mosquitoes, and the appropriate agencies that will be consulted for information about vector-borne illness in and around the test location.

19. Test day preparation
    a. Provide more detail about the preparation for and timing of the study day. Include details such as whether subjects will be reminded of the restrictions before and during the testing (and if so, how and when) and how far in advance of the field testing start time and/or at what time will subjects arrive at the test site to receive treatment.
    b. During the initial briefing and test day compliance check, research staff should remind subjects that they are free to withdraw at any time and that they will be compensated for their participation up to the time of their withdrawal.

20. Test days
    a. Subjects must be assigned randomly as control or alternate subjects. Revise the protocol to delete the provision allowing the Study Director to choose control subjects based on their proficiency using an aspirator.
    b. Subjects' skin should be examined for disqualifying conditions prior to application of the test substance and again at the end of the test period.
    c. If participants are eligible to participate in more than one test day, space apart the two test days a minimum of 72 hours to minimize discomfort to subjects.
    d. Mosquito landing pressure measured by the control subjects must be established as 5 landings within 5 minutes on **each** of the control subjects in order for EPA to consider the data reliable. It is not ethical to rely on data that are not scientifically acceptable; ensure that the protocol language for landing pressure matches the definition provided by EPA in the science review comments.
    e. If the test is moved "to a nearby location where biting pressure may be higher", the subjects should still have the same access to a screened enclosure for resting between exposure periods.
    f. Subjects should be reminded at the start of the test day that they are free to withdraw from the study at any time and without penalty, and whether/how their data would be used if they choose to withdraw after testing has begun.
    g. The EPA recommends instructing subjects to wash their treated limb as soon as possible after their participation ends and providing soap, water, and paper towels at the field site or at the facility where subjects will be returning to at the end of the testing day.

21. To confirm that subjects did not contact a vector-borne illness or suffer adverse events after the field testing, the Study Director should contact all subjects after their participation. This contact should be made after enough time has elapsed that symptoms of vector-borne illness would have appeared. If a subject reports an adverse effect that is likely related to exposure to a vector-borne illness and their participation in the test, other subjects from that test day should be notified.

22. The protocol calls for notifying the IRB within 10 days if a mosquito-borne disease is detected in the mosquitoes collected on test days (p. 17). The approval from the WCG IRB notes that "any site monitoring report that directly and materially affects subject safety or their willingness to continue participation" should be provided to the IRB within 5 days (WCG IRB Certificate of Action, 3/8/2022, p. 2). The protocol should also include a timeframe for notifying subjects in the instance any mosquito-borne illness is detected at a test site where they were present.

23. Protocol amendments and IRB oversight
    a. Revise the protocol discussion on amendments to the protocol (p. 5). Any changes to the protocol must be submitted to the IRB for review and approval **before** implementation. Amendments should not be signed and dated as effective by the study director until after receiving approval from the IRB.
    b. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided WGC IRB is notified according to its procedures.
    c. All amendments, deviations, and any adverse events must be documented in the study and reported to the WGC IRB consistent with its reporting procedures.
    d. Any changes to the protocol should be reflected in the protocol itself, rather than as a note to file or attachment.
    e. Ensure all references to the IRB overseeing the research are accurate in the protocol and consent materials. The consent form notes that Schulman Associates IRB may be contacted (p. 14).
    f. Include a statement that "**This study will be conducted in accordance with the EPA's final regulation at 40 CFR 26 that establishes requirement for the protection of subjects in human research. The protocol, informed consent form, and other required documentation for this study must be approved by an independent institutional review board and submitted to the EPA as required by 40 CFR 26.1125 before the research can be initiated. The report of the completed research is subject to the requirements at 40 CFR 26.1303 to provide documentation related the ethical conduct of the study.**"

24. COVID-19 – Include that all federal regulations/guidelines in effect will be followed, as well as a process to notify study staff and/or subjects if anyone they had contact with during the study becomes ill.

25. Confidentiality – If photos will be taken at any point during the study, revise the protocol to include a statement that any photos taken during the study will not include the

subjects' faces or identifying features, or that these elements will be blurred before the photos are distributed or published.

26. Delete or provide a rationale for allowing the Study Director or other delegated staff to "end a particular participant's participation on a test day at any time, for any reason" (Protocol, p. 22). Generally, the EPA recommends that the Study Director have limited discretion to withdraw subjects from the study as outlined in the protocol. For example, such discretion could be characterized as: "*Participants' enrollment in the study may be ended at the discretion of the Study Director where continued participation may affect the safety of the participant or where there is a development of any condition that might interfere with study participation.*"

27. Documentation
    a. The protocol should include sample data collection sheets and other forms that will be used to collect and track subject information.
    b. EPA recommends that the researchers consider the guidance from the Food and Drug Administration when drafting the final report.[8] Specifically, pages 7-9 provide a summary of how a study report should be organized and what it should contain to be free from ambiguity and to facilitate review.

Attachments:

1. EPA Protocol Review
2. Ethics Review Checklists
3. SCJ Statistical Support for Sample Size
4. EPA Power Analysis
5. Basis for EPA Recommended Standard Dose

[8] Food and Drug Administration. Guideline for Industry. Structure and Content of Clinical Study Reports. July 1996. https://www.fda.gov/media/71271/download

ATTACHMENT 1
EPA Protocol Review

Title: Science and Ethics Review of a Protocol for Efficacy Testing of SCJ Personal Repellent Products against Mosquitoes in a Field Study.

Date on Draft Protocol: February 2022

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1. Societal Value of Proposed Research

(a) What is the stated purpose of the proposed research?

The objective of this study is to determine the duration of efficacy of two different personal repellents against mosquitoes that have the potential to transmit pathogens of public health importance in a field setting using human test subjects. Efficacy will be measured as the duration between test substance application and the first confirmed mosquito landing on a test subject's treated appendage. The FCL is defined as the time at which one mosquito landing occurs and a second landing occurs within 30 minutes. The second landing confirms the first landing. The period from treatment to the FCL will be defined as the complete protection time (CPT). A median complete protection time (mCPT) will be estimated from the CPTs of the study participants for each product.

(b) What research question does it address? Why is this question important? Would the research fill an important gap in understanding?

CPT data points will be statistically analyzed to determine mCPT for both repellents individually. This information does not currently exist for the proposed product formulations containing PMD and picaridin as their active ingredient. The data generated by the proposed research will be used to characterize the proposed products' repellency duration (mCPT) in support of product registration with the EPA. The proposed study will characterize the efficacy of the products for registration, which has not yet been evaluated.

(c) How would the study be used by EPA?

The proposed study would be used to generate product-specific efficacy data which the EPA requires for registration of skin-applied insect repellents. As of this writing, the product formulations containing PMD and picaridin as an aerosol or solid stick have not yet been evaluated by the EPA regarding their performance against mosquitoes of public health importance. The data that is generated will be reviewed to assure that all requirements are met regarding use of these skin-applied insect repellents by humans and that any claims made on their label are supported.

A standardized protocol evaluated and approved by the Agency will ensure that the field testing data is generated in accordance with the appropriate EPA Guideline and Rules, namely *OPPTS 810.3700: Insect Repellents to be Applied to Human*

Skin (July 10, 2010) and the most recent Product Performance Rule which can be found at: https://www.federalregister.gov/documents/2022/04/15/2022-07963/pesticide-product-performance-data-requirements-for-products-claiming-efficacy-against-certain.

(d) Could the research question be answered with existing data? If so, how? If not, why not?

The EPA requires product-specific efficacy data to support any product registration. No previous data has been submitted or approved regarding the use of these products against mosquitoes under the proposed use pattern.

(e) Could the question be answered without newly exposing human subjects? If so, then how? If not, why not?

Humans are the target for the test products and there are currently no recognized reliable models or surrogates available for repellency testing that accurately mimic the intended use of these products on humans against mosquitoes of public health concern.

2. Study Design

(a) What is the scientific objective of the study? If there is an explicit hypothesis, what is it?

The aim of this study is to determine the duration of efficacy of two novel insect repellents, one containing 10% PMD and another containing 10% picaridin as the active ingredients against species of mosquitoes within the genera *Anopheles*, *Aedes*, and *Culex* that may pose a threat to public health. The proposed hypothesis is that the two products to be tested will prevent landings of wild mosquitoes on treated human test subjects for a given period of time to be determined by this research.

(b) Can the study as proposed achieve that objective or test this hypothesis?

The objectives may be achieved after revisions to the protocol suggested by the Agency pertaining to scientific and ethical concerns are implemented. In its current, unedited form the protocol does not likely meet the scientific and ethical standards necessary for a successful product registration with the Agency.

2.1 Statistical Design

(a) What is the rationale for the choice of sample size?

A sample size of 14 treated test subjects has been proposed for each product at each field test site. The rationale given by the sponsor (Attachment 3) is that a

sample size of 14 allows for an equal number of male and female test subjects. However, based on a power analysis, the EPA recommends a sample size of 13 test subjects when performing skin-applied repellency studies (Attachment 4), which has been simulated to provide an adequate amount of data for statistically meaningful results (i.e., appropriate statistical power) without unnecessarily subjecting additional test subjects to the treatment.

(b) What negative and positive controls are proposed? Are proposed controls appropriate for the study design and statistical analysis plan?

Two untreated test subjects, ideally a male and a female, will serve as controls for the duration of the study at each test location for each product. They are tasked with serving as potential hosts to monitor adequate landing pressure at the test site during the skin-applied repellent studies. However, results obtained by the control subjects will not be factored into statistical analyses of repellency data obtained during the field testing.

(c) How is the study blinded?

The test subjects will not be blinded as to the identity of the test substance that they are treated with, but each product will be tested separately. Study staff and subjects will know the identity of the test substances.

(d) What is the plan for allocating individuals to treatment or control groups?

There will be a total of 20 test subjects present for each product at each test location for every test day. Fourteen individuals will be randomly selected as treated test subjects, 2 as untreated control test subjects, and 4 as alternates. It is stated that the Study Director or Principal Investigator will randomly select an equal number of male and female treated, control, and alternate test subjects based on assigned coded numbers, but this process is not described in sufficient detail.

(e) Can the data be statistically analyzed?

Yes. See (f) below.

(f) What is the plan for statistical analysis of the data?

The mCPT of all test subjects at two test sites for both products will be calculated using the Kaplan-Meier estimator. EPA recommends the duration of protection for each repellent product to be the lowest mCPT of tests conducted at two ecologically distinct sites. For labeling purposes, the Agency rounds down mCPT values to the nearest whole number. For example, three hours and 45 minutes would be listed on the label as three hours. Additional information regarding statistical analysis can be found in the Repellency Awareness Guidance For Skin-

Applied Insect Repellent Producers at: https//www.regulations.gov/document/EPA-HQ-OPP-2013-0406-0003.

(g) Are proposed statistical methods appropriate to answer the research question?

The mCPT will be estimated from the CPTs of study participants using the Kaplan-Meier estimator. This method allows the use of non-parametric data, which is not uncommon with this type of testing where the CPTs may not be normally distributed. The Kaplan-Meier estimator has been accepted by EPA and the HSRB for past skin-applied repellent studies and is the recommended method by the EPA when compared to less conservative parametric methods (i.e., Weibull and Normal).

(h) Does the proposed design have adequate statistical power to definitively answer the research question?

The proposed sample size of 14 subjects has adequate statistical power based on the results of EPA and registrant simulations. The EPA's recommended sample size of 13 also has adequate statistical power and minimizes the number of individuals needed for testing. For more detailed information on the statistical simulation see Attachment 4.

2.2 How and to what will human subjects be exposed?

During the field efficacy studies, test subjects will be exposed to a 10% picaridin solid stick or a 10% PMD aerosol formulation. It is currently unclear if the same test subjects will have the ability to participate in more than one test on a different day. The aerosol product containing 10% PMD will be applied at a dose of 1.0 g product/600 cm^2 of skin to either a test subject's arm or leg. Dosimetry testing in a laboratory or at a field site will be performed for the solid stick picaridin formulation before any field efficacy testing is performed and it was reported that no test subjects would be allowed to treat themselves with more than 2.0 g product/600 cm^2 during dose determination testing. Field exposure time was reported as potentially 12+ hours for each day of testing per subject, but the Agency recommends a cutoff number of hours. In the field, subjects will be exposed to natural mosquito populations relevant to public health where pathogens have not been detected for at least one month prior to testing. In the laboratory during pre-test attraction testing and aspirator training, participants will be exposed to lab-reared mosquitoes that have not taken a blood meal.

(a) What is the rationale for the choice of test material and formulation?

Efficacy data are required to characterize product performance and support efficacy claims against mosquitoes on product labels. EPA requires submission

of product performance data for registration of all products claiming efficacy against public health pests.

(b) What is the rationale for the choice of dose/exposure levels and the staging of dose administration?

Based on an analysis of dosimetry results from repellent studies reviewed by EPA and HSRB since 2006, EPA considers a dose of 1.0 g product/600 cm^2 of skin to be an appropriate product dose for testing aerosols, wipes, and lotion type products and 0.5 g (± 10%) product/600 cm^2 of skin for testing pump spray type products. EPA does not have a recommended dose for use with the solid stick product based on existing dosimetry data, so dose determination testing to establish a typical consumer dose will take place for the picaridin product before field studies begin.

(c) What duration of exposure is proposed?

Dosimetry will only be performed for the picaridin solid stick. In the laboratory (for dosimetry), test subjects will be instructed to apply the test product to their own arm or leg based on proposed labeling directions. This dose determination testing will occur presumably over a matter of minutes, but the duration was not explicit in the proposed protocol. Exposure time in this instance will be comprised of the time is takes to apply the product to achieve complete coverage and then washing the product off once sufficient application is completed.

Field testing was described as potentially taking 12+ hours per day, but no cutoff time was established. Repellency testing for each product will take one day per field site per test subject, but it is unclear if both products will be tested on the same day at the same site. Exposure time will begin when the product is sprayed (PMD aerosol) or wiped onto the test subject (picaridin stick) and will end when the FCL occurs. The period from treatment to the FCL will be defined as the CPT.

Proposed exposure periods consist of exposing treated skin to field mosquitoes for 5 minutes at 30-minute intervals until CPT is reached by the treated test subjects or end of pre-determined test day occurs, whichever happens sooner. Control test subjects will monitor landing pressure at the test site by exposing an untreated limb to wild mosquitoes for 5 minutes or less until 5 landings have occurred. The test for monitoring landing pressure with control test subjects will always precede efficacy testing by the treated test subjects.

2.3 Endpoints and Measures

(a) What endpoints will be measured? Are they appropriate to the question(s) being asked?

Efficacy will be measured as the duration between test substance application and the first confirmed mosquito landing on a test subject's treated appendage. The first confirmed landing is defined as the time at which one mosquito landing occurs and a second landing occurs within 30 minutes. The second landing confirms the first landing. The period from treatment to the first confirmed landing will be defined as the CPT. A mCPT will be estimated from the CPTs of the study participants using the Kaplan-Meier estimator for each product. The endpoints are appropriate for the question being asked.

(b) What steps are proposed to ensure measurements are accurate and reliable?

- Compliance with Good Laboratory Practices (GLP) as defined by 40 CFR 160.
- Specific inclusion and exclusion criteria will be established and followed closely so that testing will be performed on a representative population of insect repellent users in the United States.
- A standard dose of 1.0 g product/600 cm^2 of skin will be used for the PMD aerosol testing as suggested by the Agency; a dose determination test (dosimetry) will be conducted in the laboratory for the picaridin stick product.
- Limb measurements will be conducted to calculate the appropriate treatment area for each test subject.
- Test subjects will be identified by numbers that will be used to randomly select for the various groups and products that are being tested. However, the randomization details need to be discussed in more detail in a revised protocol.
- Training in the laboratory will be performed to assess a candidate's attractiveness to lab-reared mosquitoes. Candidates that are deemed unattractive (not receiving an adequate number of landings within a given time) will not participate in further training or testing.
- Training in the laboratory will be performed to instruct test subjects on how to properly aspirate lab-reared mosquitoes after they have landed on their skin, but before they are able to bite. However, further details will need to be provided in a revised protocol that describe the specific criteria at which a test subject is sufficiently proficient to participate in field testing.
- Lab-reared mosquitoes used for attractiveness testing and aspirator training will be certified pathogen-free and readily available for the number of replicates deemed necessary to assess attractiveness and achieve sufficient proficiency.
- Fourteen test subjects, half male and half female, will be treated with the product (either the PMD aerosol or picaridin stick) and exposed to wild mosquitoes until the first confirmed landing for the product occurs.
- Two control test subjects, preferably one male and one female, will serve to monitor adequate mosquito landing pressure each day of testing for each product.

- Four alternate test subjects will be available for each day of testing in case a test subject has to withdraw from the study at any time for any reason.
- Efficacy testing will be conducted at two ecologically distinct sites where the predominant mosquito species of public health interest differs between sites, and the required representative species are present. Mosquito surveillance and pathogen testing will occur to ensure that pathogens are not detected at field sites at least one month prior to efficacy testing.
- Mosquitoes that land on any of the test subjects on the exposed limb over the duration of the field study will be collected for further analysis with regards to taxonomical identification and pathogen screening.
- A Quality Assurance Unit will inspect at least one phase of the testing to ensure the integrity of the study.
- A final report will be reviewed against the protocol, SOPs, and raw data for accuracy.

(c) What QA methods are proposed?

The Quality Assurance Unit will inspect at least one phase to ensure the integrity of the study. In addition, the final report will be reviewed against the protocol, SOPs, and raw data for accuracy. A statement will be included in the report specifying inspection dates, phases, and the dates findings were reported to the Study Director and Management.

(d) How will uncertainty be addressed? Will point estimates be accompanied by measures of uncertainty?

Sources of variation include mosquito species and activity at two ecologically distinct sites, and attractiveness of subjects to mosquitoes. These uncertainties will be addressed by control subjects monitoring landing pressure throughout the test, by determination of a subject's attractiveness to mosquitoes prior to efficacy testing, and by using the lowest (most conservative) mCPT per product per field site for the duration of efficacy evaluation.

3. Subject Selection

3.1 Representativeness of Sample

(a) What is the population of concern?

The population of concern is any person that would purchase and use a skin-applied insect repellent to protect themselves from mosquito bites in the United States.

(b) From what populations will subjects be recruited?

Test subjects will be recruited from a population of healthy males or females, ages 18-55, in the United States. Presumably, a representative population will be selected close to the Wisconsin and Massachusetts testing sites since participants are responsible for their own transportation to and from the testing site, but this information was not specified in the protocol. The protocol indicates that an equal number of male and female participants is desired.

(c) Are expected participants representative of the population of concern? If not, why not?

Yes. The recruitment information provided in the protocol indicates that the selection criteria is consistent with the specific population of concern.

(d) Can the findings from the proposed study be generalized beyond the study sample?

Yes. The study will include a statistically adequate number of replicates for each product at each test site. The field test sites will be ecologically distinct sites where the predominant species differ and are representative of the appropriate *Anopheles*, *Aedes*, and *Culex* species required for mosquito repellency claims as per the in the Product Performance Rule (published 4/15/22). Power analysis is employed for estimation of adequate sample size to calculate a reliable estimate of mCPT, and the randomization plan requires maintaining an even distribution of male and female test subjects to each treatment group.

3.2 Equitable Selection of Subjects

(a) What are the inclusion/exclusion criteria? Are they complete and appropriate?

The eligibility criteria are included on pages 3-4 of the protocol. They include:

Inclusion Criteria
1. *Must be between ages 18-55 and provide proof of age by a driver's license, passport, or other valid identification*
2. *Must read and understand English*
3. *Must not be employees of SC Johnson or immediate family members of SC Johnson employees*
4. *Must have a reliable form of transportation to get to and from the test and training locations. Subjects are responsible for their own transportation to and from the training and test locations*
5. *Must be willing to be exposed to and potentially bitten by mosquitoes. Must not be known to be hypersensitive to mosquito bites. All measures possible will be taken to prevent mosquito bites.*

6. *Must be willing to refrain from using alcohol 12 hours before the test, and refrain from nicotine, and fragrance products (e.g., soap, perfume, cologne, hair spray, lotion, etc.) during the test*
7. *Must be willing to follow the study procedures as explained and be willing to sign an ICD*
8. *Due to Covid-19, Subjects must be willing to have their temperature checked via a contactless infrared digital thermometer prior to participating each training or test day(s).*
9. *Must be a user of insect repellent products*

Exclusion Criteria
1. *Sensitivity or allergy to mosquito bites, Elastikon (or equivalent) tape, latex insect repellents, or skin care products*
2. *Suffer from respiratory problems such as asthma*
3. *Currently suffering skin disease or skin problems, such as eczema, psoriasis, or atopic dermatitis*
4. *Health conditions or any health concerns that would make them unable to remain outdoors, in a suit made of tightly woven material that a mosquito's proboscis cannot penetrate (a bug suit), for several hours where high temperatures, high humidity and sweating are likely to occur*
5. *Health conditions or any health concerns that would make them unable to sit in a chair for long periods, with breaks for limb stretching and movement at reasonable intervals, or unable to stand continuously for five minutes in conditions where high temperatures, high humidity and sweating are likely*
6. *Female subjects must not be pregnant or breast-feeding. Female test subjects will be required to take a pregnancy test whenever they will be exposed to the test substance or mosquitoes. Female test subjects will be required to arrive at the test location at an earlier time than the male subjects. At this time a female study staff member will discuss with each female subject whether a pregnancy test will be needed Any female subject that affirms they are naturally or surgically incapable of pregnancy will not be required to take a pregnancy test. For those female subjects that could potentially be pregnant, it will be required to perform an over-the-counter pregnancy test the day of the test. The pregnancy test will be supplied by the Sponsor. The test will be performed by each test subject alone in a private bathroom. After completion of the pregnancy test, a female member of the study staff will ask each female test subject separately in a private setting, away from all other people, if the potential subject is still interested in participating in the study. If the test is negative and the test subject is interested in participating, the results will be verified by a female of the study staff in a private manner.*

These criteria are also included on pp. 19-20 of the protocol. EPA has recommended the addition and clarification of some eligibility criteria.

The eligibility criteria limit the participation of subjects to English speakers. Though the research does not offer benefits to subjects, enrolling non-English speakers would make the study enrollment more equitable.

(b) What, if any, is the relationship between the investigator and the subjects?

There should be no relationship between the investigator and subjects beyond their interactions as part of the research study. Those who are employees of SC Johnson or immediate family members of SC Johnson employees are prohibited from participating in the study (p. 3).

(c) Will subjects be recruited from a vulnerable population?

The protocol states "*no one categorized as 'vulnerable' will be considered in this placement*" (p. 4).

Recruitment will be conducted in two different locations within the United States, and will be conducted by independent recruitment firms. The recruitment target is to assemble a pool of potentially eligible subjects who represent the demographics of users of skin-applied mosquito repellents. The EPA does not believe that based on the protocol and recruitment plan, recruitment will target subjects from vulnerable populations.

(d) What process is proposed for recruiting and informing potential subjects?

The protocol notes that "*subjects will be recruited from the general public by an independent recruitment agency with the goal that the pool closely represents the general demographics of repellent users in North America, aiming for an equal number of male and females*" (p. 4). "*The recruitment firms will contact subjects via internet platforms following the screening document approved by the IRB. Potential subjects will be given a brief outline of the study, their role in the study, and the inclusion exclusion [sic] criteria. If they meet the criteria and are interested in potentially enrolling in the study, they will notify the recruitment firm and they will be scheduled to attend a test subject training session lead by the SCJ study staff*" (pp. 18-19).

The protocol is unclear how exactly subjects will be recruited, only noting that subjects will be contacted by email by the recruitment firm. No advertisements or other recruitment materials beyond the email template were provided. EPA has made recommendations regarding the recruitment process and the manner in which subjects are informed about the study that should be addressed before the research is initiated.

(e) If any subjects are potentially subject to coercion or undue influence, what specific safeguards are proposed to protect their rights and welfare?

Subjects will be recruited by independent recruitment agencies, minimizing the potential for coercion or undue influence related to the decision about whether to participate in the study. In addition, employees of the study sponsor and employees' immediate family members are excluded from participation, safeguarding this group from undue influence to participate in the study.

Employees of the research firms and any other organization associated with conducting this research study, as well as their family members, should also be excluded from participation in the study in order to avoid any appearance of coercion or undue influence to enroll.

3.3 Remuneration of Subjects

(a) What remuneration, if any, is proposed for the subjects?

The protocol notes that subjects will be compensated for their time spent participating in the study as follows: $100 for the participating in the training meeting and $35 per hour (rounded up to the next hour) for participation in a test day. If the test day is postponed due to weather, subjects who were available for the test day will be compensated $60 for being available and will be invited to participate on the rescheduled test day. Alternates who are asked to show up at the test site will be paid $100 for their time (p. 13). Subjects who participate in the dose determination study will be compensated $100 for their participation in session, which is expected to last 2 hours (p. 22).

(b) Is proposed remuneration so high as to be an undue inducement?

No, the remuneration is reasonable in light of the burden and inconvenience associated with participated in the study.

(c) Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects?

No. The rates seem reasonable for the burden associated with spending 12 plus hours in a hot, humid environment and subjecting oneself to mosquitoes.

(d) How and when would subjects be paid?

Subjects will receive their compensation by check or prepaid gift card from the independent recruitment agencies. The protocol is unclear when compensation will be provided – either at the end of every subject interaction with the study team, or at the conclusion of their participation. The EPA has requested that this information be included in the protocol.

4. Risks to Subjects

4.1 Risk characterization

(a) Have all appropriate prerequisite studies been performed? What do they show about the hazards of the test material?

One of the test materials is a spray product that contains 10% PMD. A 90-Day dermal study in rats (MRID 44438710 ~~10~~) tested PMD (98.3 % pure) at increasing doses, 0, 1,000 and 3,000 mg/kg/day. The NOAEL = 1,000 mg/kg/day, and the LOAEL = 3,000 mg/kg/day. The endpoints for NOAEL and LOAEL are based on treated skin observations, erythema, edema, eschar, and histological observations in treated skin, increased acanthosis and inflammation at the highest dose of 3,000 mg/kg/day. No dermal absorption data are required for Tier I Toxicity data for registration of biochemical products. Therefore, without these data, dermal absorption is assumed to be 100%. Risk characterization for infants and children is based on data from one developmental study (MRID 44438711) in which the NOAEL = 3,000 mg/kg/day. No LOAEL was established, and thus, a 10-fold safety factor is applied for risk characterization. MOEs were not calculated because there are no endpoints of concern for the dermal route of exposure. The Agency concluded that there is reasonable certainty of no harm to populations or subpopulation (infants and children) from the use of PMD in insect repellent products applied to human skin.

The other test material is a solid stick product containing 10% picaridin. The active ingredient picaridin is classified as toxicity category IV for Acute Oral (LD_{50} >5,000 mg/kg (MRID 51868905 and 44408748), Acute Dermal (LD_{50} >5,000 mg/kg (MRID 51868907 and 44408749), Acute Inhalation (LC_{50} > 4.364 mg/L (could be waived based on results from MRID 44408709), and Dermal Irritation (MRID 51868902). It is classified as toxicity category III for Eye Irritation (i.e., caused moderate eye irritation that cleared in 7 days or less; MRID 51868903) and is not a dermal sensitizer (MRID 51868906 and 44408752). MOEs were not calculated because there are no endpoints of concern for the dermal route of exposure. The entire chronic toxicity database was generated using dermal studies, including developmental/reproductive and chronic studies, and there were no systemic toxic effects identified that would be relevant to humans. In the acute dermal study, the LC_{50}, NOEL and NOAEL were all greater than 2,000 mg/kg, and there was no evidence of dermal irritation or dermal sensitization. The Agency concluded that there is reasonable certainty of no harm to populations or subpopulation (infants and children) from the use of picaridin in insect repellent products applied to human skin.

(b) What is the nature of the risks to subjects of the proposed research?

Risks to test subjects include the risk of exposure to field mosquitoes and mosquito-borne pathogens, the risk of exposure to the test materials, risks related to receiving an unexpected result on a pregnancy test, health risks associated with sitting and standing outdoors in areas with elevated temperature and humidity for several hours, and the risk of a loss of confidentiality.

(c) How do proposed dose/exposure levels compare to the established NOAELs for the test material?

The spray product contains 10% PMD. Primary dermal irritation study (MRID 44438704) using 98.3 % pure PMD shows the test material to be non-irritating after 4 hours of exposure. Erythema cleared in 72 hours for 4 out of 6 rabbits. No traces of irritation was observed after 7 days. Acute dermal toxicity study using 98% PMD (MRID 44438702) applied at a dose of 5,000 mg/kg reports LC_{50} > 5,000 mg/kg. The dose applied for testing is 1 g/600 cm^2/day, lower than the NOAEL = 1,000 mg/kg/day, and the LOAEL = 3,000 mg/kg/day of 98.3 % PMD. The endpoints for NOAEL and LOAEL are based on treated skin observations, erythema, edema, eschar, and histological observations in treated skin, increased acanthosis and inflammation at the highest dose of 3,000 mg/kg/day. These values are based on a 90-Day dermal study in rats (MRID 44438710) that tested PMD (98.3 % pure) at increasing doses of 0, 1,000 and 3,000 mg/kg/day.

The active ingredient picaridin is classified as toxicity category IV for Acute Oral (LD_{50} >5,000 mg/kg (MRID 51868905 and 44408748), Acute Dermal (LD_{50} >5,000 mg/kg (MRID 51868907 and 44408749), Acute Inhalation (LC_{50} > 4.364 mg/L (could be waived based on results from MRID 44408709), and Dermal Irritation (MRID 51868902). It is classified as toxicity category III for Eye Irritation (i.e., caused moderate eye irritation that cleared in 7 days or less; MRID 51868903) and is not a dermal sensitizer (MRID 51868906 and 44408752). MOEs were not calculated because there are no endpoints of concern for the dermal route of exposure. The entire chronic toxicity database was generated using dermal studies, including developmental/reproductive and chronic studies, and there were no systemic toxic effects identified that would be relevant to humans. In the acute dermal study, the LC_{50}, NOEL and NOAEL were all greater than 2,000 mg/kg, and there was no evidence of dermal irritation or dermal sensitization. The Agency concluded that there is reasonable certainty of no harm to populations or subpopulation (infants and children) from the use of picaridin in insect repellent products applied to human skin.

(d) What is the probability of each risk associated with the research? How was this probability estimated?

No numerical probability is estimated, but risks have a low probability of occurrence. Practical steps to minimize test subject risks are described in the protocol.

4.2 Risk minimization

(a) What specific steps are proposed to minimize risks to subjects?

The protocol outlines the risks and how they will be minimized on pp. 20-22. These include:

- Employing the eligibility criteria to minimize the risk of adverse reaction to the test substance and mosquito bites
- Monitoring the field sites in advance of the test days and coordinating with state and local agencies to confirm that no mosquito-borne disease is present at the test site
- Training subjects on the proper use of an aspirator to capture mosquitoes that land before they can bite
- Informing subjects about the symptoms of mosquito-vectored diseases so they can be identified, and subjects can seek medical attention if they experience them
- Confirming the attractiveness of individuals to mosquitoes prior to their participation in the field test
- Protecting the privacy of female subjects during pregnancy testing
- Maintaining the confidentiality of subjects' identities
- Providing a shaded area, seating, cool drinks, and snacks for the subjects to use between exposure periods
- Providing common over-the-counter first aid items (bandages, antiseptics, antihistamines) to subjects upon request
- Providing qualified first aid assistance and transporting injured/ill subjects to the closest facility for medical attention

The proposed risk mitigation measures seem reasonable, though incomplete. EPA has recommended additional steps that should be taken to effectively minimize the identified risks to subjects in this study.

(b) What stopping rules are proposed in the protocol?

- Each subjects' participation will stop when they experience FCL.
- "*If adequate landing pressure on the control subjects is not achieved during 3 consecutive exposure periods, the test will be stopped for all test subjects*" (p. 29).
- "*If adverse reactions are observed during the test, the test subject will be removed from the test immediately*" (p. 30).
- "*The Study Director or PI will stop, and if needed reschedule, the test day if temperatures exceed 100°F, or other unanticipated weather arises that poses unsafe conditions to remain outdoors*" (p. 30).

(c) How does the protocol provide for medical management of potential illness or injury to subjects?

Medical management will be provided through a combination of first aid supplies available at the field site, as well as transportation to the closest hospital in the event of a serious incident. Additionally, subjects will be instructed to monitor for symptoms of mosquito-borne illness and to seek medical attention in the event they experience such symptoms.

(d) How does the protocol provide for post-exposure monitoring or follow-up? Is it of long enough duration to discover adverse events which might occur?

The protocol does not specify a period for post-exposure monitoring or follow-up. The EPA has proposed including a provision requiring the Study Director to contact each subject after their participation at an interval that is of long enough duration to discover any adverse events that might occur.

The protocol includes a provision for the Study Director to notify subjects if diseases are identified in the mosquitoes collected in the field during each day of the field testing.

(e) How and by whom will medical care for research-related injuries to subjects be paid?

The consent form notes "*In the unlikely event that you are injured as a result of your participation in this study, medical care will be made immediately available. The sponsor will reimburse you for the costs of this care.*" (p. 13)

The EPA has recommended that this information and more details about the process for reimbursement be included in the protocol.

5. Benefits

(a) What benefits of the proposed research, if any, would accrue to individual subjects?

No benefits would accrue to the subjects.

(b) What benefits to society are anticipated from the information likely to be gained through the research?

Depending on the results of the research, it may benefit society by generating reliable repellency efficacy data that could be used by the EPA to register insect repellent products containing the ingredients tested. Registration of effective repellent products could lead to fewer mosquito bites and reduced incidents of vector-borne illnesses.

(c) How would societal benefits be distributed? Who would benefit from the proposed research?

Users of skin-applied repellents would benefit from the results of this research through availability of effective products.

The Sponsor would benefit through registration of the products, which would allow sale and distribution within the United States.

(d) What is the likelihood that each identified societal benefits would be realized?

If the protocol is modified to address adequately all of the EPA's recommendations, then it is likely the study will meet applicable scientific and ethical standards, could be used to register the product, and would result in the potential sale of additional skin-applied repellent products to users.

6. Risk/Benefit Balance

(a) How do the risks to subjects weigh against the anticipated benefits of the research, to subjects or to society?

The protocol describes a procedure for generating scientifically sound data and includes measures to limit the risks to subjects participating in the study. With the risk mitigation measures put in place and provided that the EPA's comments addressed, the remaining risk to subjects is low and reasonable in light of the potential benefits of the data to society.

7. Independent Ethics Review

(a) What IRB reviewed the proposed research?

Western Copernicus Group IRB

(b) Is this IRB independent of the investigators and sponsors of the research?

Yes

(c) Is this IRB registered with OHRP?

Yes

(d) Is this IRB accredited? If so, by whom?

Yes, WCG IRB is accredited by the Association for the Accreditation of Human Research Protection Programs.

(e) Does this IRB hold a Federal-Wide Assurance from OHRP?

Yes

(f) Are complete records of the IRB review as required by 40 CFR 26.1125 provided?

Yes

(e) What standard(s) of ethical conduct would govern the work?

This is a protocol for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to the EPA under the pesticide laws. The primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply.

8. Informed Consent

(a) Will informed consent be obtained from each prospective subject?

Yes

(b) Will informed consent be appropriately documented, consistent with the requirements of 40 CFR 26.1117?

Yes, with the EPA's recommendation to amend the protocol to ensure that each subject will automatically receive a signed copy of the consent form incorporated.

(c) Do the informed consent materials meet the requirements of 40 CFR 26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research?

With the EPA's recommendations regarding the consent form, as well as all amendments to the protocol that would impact the consent process or documentation addressed, the informed consent materials are likely to meet the requirements of 40 CFR 26.1116.

(d) What is the literacy rate in English or other languages among the intended research subjects?

All subjects are required to read and understand English.

(e) What measures are proposed to overcome language differences, if any, between investigators and subjects?

None.

(f) What measures are proposed to ensure subject comprehension of risks and discomforts?

The protocol does not include measures to ensure subject comprehension of the risks and discomforts of participating or other aspects of their participation. The EPA has made a recommendation for measures to be included in the protocol.

(g) What specific procedure will be followed to inform prospective subjects and to seek and obtain their consent?

"*Prior to participating in any aspect of the test, each potential subject who has expressed interest in participation in the study and has met the inclusion/exclusion criteria will be asked to review and be willing to sign an ICD. Only the subjects that are willing to sign the ICD will be scheduled for a training date and any test date(s). Only the subjects that sign the ICD will participate in the study. Subjects will be informed that they may withdraw from testing at any time for any reason.*

"7.4.1. At the training session the Study Director or Principal Investigator (PI) will provide copies of the ICD, review the inclusion/exclusion criteria with the participants and ask if they have any questions. Any questions will be answered.

"7.4.2. If a subject still wishes to enroll in the study and meets the criteria, he or she will be asked to sign the ICD. His or her signature will be witnessed by the Study Director or PI. A copy of the signed ICD will be offered to each subject." (p. 19)

(h) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?

Subjects will be informed multiple times throughout the process that they are free to withdraw at any time without forfeiting any compensation or benefit to which they are entitled. Employees of the sponsor and employees' immediate family members are excluded from participation to avoid the perception of pressure to participate in the study. The EPA recommends also excluding employees of the recruitment firms and immediate family members of the employees for the same reason.

9. Respect for Subjects

(a) How will information about prospective and enrolled subjects be managed to ensure their privacy?

"• *Each subject will be assigned a code number. Only subjects' code numbers will appear on data sheets. The subjects' names will not appear in the report*.

"• *The report (as well as all study-related records) will not be publicly available and will be kept as confidential as possible under local, state, and federal laws and regulations. The study results generated following this protocol are not intended for publication; however, if any of the study-related data are published, subjects' identities will remain confidential*.

"• *The study records will be maintained at the study site in locked cabinets and electronic files kept on a password-protected computer server*.

"• *No one outside SC Johnson, the study staff, the recruitment firm, the IRB, or certain governmental agencies (such as USEPA) will have access to subjects' personal information*." (pp. 21-22)

(b) How will subjects be informed of their freedom to withdraw from the research at any time without penalty?

During the recruitment, consent process, training on aspirator use and attractiveness testing, and on each study day, subjects will be reminded of their freedom to withdraw at any time without penalty.

(c) How will subjects who decline to participate or who withdraw from the research be dealt with?

Individuals who decline to participate in the research do not have provide consent. Subjects who withdraw from the research will be compensated based on the length of their participation prior to the withdrawal.

The EPA recommends that the protocol include specific provisions for how the data from withdrawing subjects will be handled.

ATTACHMENT 2
Ethics Review Completeness Checklists

The following checklists are public documents. They are used by EPA in reviewing proposed protocols for third-party research involving intentional exposure of human subjects to a pesticide, with the intention of submitting the resulting data to EPA under FIFRA. These checklists only address ethical requirements and do not address the scientific integrity of the proposed study.

Checklist Associated with 40 CFR 26.1125
Submission of proposed human research for EPA review

Requirement	Y/N	Comments/Page Refs
All information relevant to the proposed research specified by §26.1115(a)		
(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, and progress reports submitted by investigators, and reports of injuries to subjects.	Y	
(2) Minutes of IRB meetings . . . in sufficient detail to show • attendance at the meetings; • actions taken by the IRB; • the vote on these actions including the number of members voting for, against, and abstaining; • the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.	Y	Provided to EPA directly by WCG IRB
(3) Records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in §26.1109(f)(1).	N/A	
(4) Copies of all correspondence between the IRB and the investigators.	Y	
(5) A list of IRB members in the same detail as described in §26.1108(a)(2).	Y	
(6) Written procedures for the IRB in the same detail as described in §26.1108(a)(3) and (4).	Y	Provided to EPA directly by WCG IRB
(7) Statements of significant new findings provided to subjects, as required by §26.1116(c)(5).	N/A	
The following additional information, to the extent not already included. A discussion of:		
(a)(1) The potential risks to human subjects	Y	
(a)(2) The measures proposed to minimize risks to the human subjects	Y	
(a)(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	
(a)(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	
(a)(5) The balance of risks and benefits of the proposed research.	Y	
(b) All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	

(c) Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	All recruitment tools and scripts must be provided to EPA before the research is initiated.
(d) A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.	Y	
(e) All correspondence between the IRB and the investigators or sponsors.	Y	
(f) Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.	Y	

Checklist Associated with 40 CFR §26.1116
General requirements for informed consent of human subjects

Criterion	Y/N	Comment/Page Reference
Consent Process – 40 CFR 26.1116(a)		
(1) Before involving a human subject in research covered by this subpart, an investigator shall obtain the legally effective informed consent of the subject.	Y	
(2) An investigator shall seek informed consent only under circumstances that provide the prospective subject sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence.	Y	Provided EPA's recommendations are addressed.
(3) The information that is given to the subject shall be in language understandable to the subject.	Y	
(4) The prospective subject must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.	Y	Provided EPA's recommendations are addressed.
(5) (i) Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. (ii) Informed consent as a whole must present information in sufficient detail relating to the research and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's understanding of the reasons why one might or might not want to participate.	Y	Provided EPA's recommendations are addressed.
(6) No informed consent may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.	Y	
Basic Elements of Informed Consent – 40 CFR 26.1116(b) In seeking informed consent the following information shall be provided to each subject:		
(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental	Y	Provided EPA's recommendations are addressed.
(2) A description of any reasonably foreseeable risks or discomforts to the subject	Y	Provided EPA's recommendations are addressed.
(3) A description of any benefits to the subject or to others that may reasonably be expected from the research	Y	
(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	N/A	
(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	Y	
(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained	Y	Provided EPA's recommendations are addressed.
(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research- related injury to the subject	Y	

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; and	Y	
(9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens: (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject, if this might be a possibility; **or** (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.	N	To be added per EPA's recommendation.
Additional elements of informed consent – 40 CFR 26.1116(c) One or more of the following elements of information, when appropriate, shall also be provided to each subject		
(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) that are currently unforeseeable;	Y	
(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;	Y	
(3) Any additional costs to the subject that may result from participation in the research;	N/A	
(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;	Y	Provided EPA's recommendations are addressed.
(5) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;	N/A	
(6) The approximate number of subjects involved in the study;	Y	
(7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;	N/A	
(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and	N/A	
(9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (*i.e.,* sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).	N/A	
(h) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function.	Y	Provided EPA's recommendations are addressed.

Checklist associated with 40 CFR §26.1117
Documentation of informed consent

Criterion	Y/N	Comment/Page Reference
(a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed (including in an electronic format) by the subject. A written copy shall be given to the subject.	Y	Provided EPA's recommendations are addressed.
(b) The informed consent form may be either of the following:		
(1) A written informed consent form that meets the requirements of §26.1116. The investigator shall give the subject adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject.	Y	Provided EPA's recommendations are addressed.
(2) A short form written informed consent form stating that the elements of informed consent required by §26.1116 have been presented orally to the subject, and that the key information required by §26.1116(a)(5)(i) was presented first to the subject, before other information, if any, was provided. The IRB shall approve a written summary of what is to be said to the subject. When this method is used, there shall be a witness to the oral presentation. Only the short form itself is to be signed by the subject. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary must be given to the subject, in addition to a copy of the short form.	N/A	

ATTACHMENT 3
S.C. Johnson Statistical Analysis to Support Sample Size

Provided as a separate file

ATTACHMENT 4

Power/Sample Size Calculation for Mosquito Repellency Studies where Complete Protection Time is the Endpoint

Date: 11/20/2017

Objective

To determine the sample size N such that mosquito repellency studies have sufficient power to obtain a given degree of **precision** in the estimate of median Complete Protection Time (mCPT). This precision – designated as "K" -- will be expressed as the ratio: 95% LCL_{mCPT}/estimated mCPT.

The simulation used to estimate varying sample sizes will require that that 95% LCL_{mCPT}/estimated mCPT<K; the true **variation** of the Complete Protection Time (CPT) distribution will be expressed by the Weibull distribution family and a parameter, P5MR, defined as the 5^{th} percentile/mCPT.

In order to develop estimates of a required sample size for a mosquito repellency study to achieve certain stated efficacy criteria and estimate a complete protection time (CPT)[9], it is necessary to determine the distribution of mosquito repellent failure times (generally considered to be time to first landing with intent to bite). However, the underlying distribution of the CPT of a product being tested in a mosquito repellency study is not known prior to the testing phase. What is known about the distribution is that CPT values are (necessarily) non-negative and are (generally) right censored after 10 (or 12 hours) in most mosquito repellency studies.

On this basis, EPA assumed for this sample size determination exercise that a distribution of mosquito repellent failure times follows a Weibull distribution. A Weibull distribution is commonly used in reliability engineering and failure analysis, in survival analysis, in predicting delivery times, in weather forecasting and hydrology, and in extreme value prediction. Its utility in a wide variety of applications is due in part to its flexibility to take on a variety of shapes depending on the parameters selected to describe the distribution. Oftentimes, the Weibull plot is described by two parameters: κ (the "shape" parameter and sometimes referred to in some parameterizations as "a") and λ (the scale parameter and sometimes referred to as "b").[10] The PDF (probability density function) and CDF (cumulative distribution function) of the aforementioned two-parameter Weibull distribution are defined, respectively, as follows:

[9]The Complete Protection Time (CPT) is defined as the time from initial application of the repellent by the test subject to the time of first confirmed landing with intent to bite (FCLIB). The FCLIB is considered to be when one landing is followed by another landing within 30 minutes. The first landing is confirmed by the second landing.

[10]A Weibull distribution can sometimes be described by 3 parameters, with a "location" parameter added as a third parameter to the "scale" and "shape" parameter of the 2-parameter Weibull distribution.

$$f(x, \boldsymbol{\kappa}, \lambda) = \begin{cases} \frac{\boldsymbol{\kappa}}{\lambda}\left(\frac{x}{\lambda}\right)^{\boldsymbol{\kappa}-1} e^{-(x/\lambda)^{\boldsymbol{\kappa}}} & x \geq 0, \\ 0 & x < 0 \end{cases}$$

$$F(x, \boldsymbol{\kappa}, \lambda) = \begin{cases} 1 - e^{-(x/\lambda)^{\boldsymbol{\kappa}}} & x \geq 0, \\ 0 & x < 0 \end{cases}$$

and are illustrated in the associated plots in Figures 1 and 2 for some illustrative **κ** and λ values.

Parameterizing the Weibull distribution in terms of **κ** and λ is, however, not necessarily intuitive with respect to studying – and judging -- the efficacy of skin-applied mosquito repellents as measured by CPT for individuals using the repellent in the field. Instead, it is more natural and desirable to be able to express the efficacy of the repellent in terms of both the expected precision of the estimated median CPT (mCPT) and in terms of the estimated variability of mCPT in (or across) the population. More specifically: the testing of a given repellent in the field should be able to generate a reasonably precise estimate of the mCPT that is expected to be generally close to what a sizable fraction of the population would be expected to experience (or, more accurately, a mCPT that only a small fraction of the population would ideally experience to be much shorter).

Following the above logic, we define the *precision of the CPT estimate* -- designated as "K" -- as follows:

$K = 95\%\ LCL_{mCPT}$/estimated mCPT

where: mCPT= median complete protection time
$95\%\ LCL_{mCPT}$ = 95% lower confidence limit on the estimated mCPT

Similarly, the degree of variation of the CPT distribution in the population will be defined as the P5MR which we define here as the ratio between the mCPT of the 5th percentile of the population to the mCPT of the population:

$P5MR = CPT_{5th\ \%ile}$ /mCPT

where: mCPT= median complete protection time
$CPT_{5th\ \%ile}$ = 5th percentile of the distribution of CPT

Re-parameterization of Standard Weibull Equation

While the above mCPT and P5MR parameterizations of the Weibull distribution are intuitively appealing for judging and evaluating repellent efficacy, they are non-standard parameterizations and it is necessary -- for comparison and simulation purposes -- to convert these to the more standard **κ** (shape) and λ (scale) values. To do this, EPA developed an equation such that interconversion between the standard (***κ*** (shape) and λ (scale)) parameterization of the Weibull to this alternate version (with the Weibull distribution instead expressed in terms of P5MR and mCPT). Briefly, the cumulative probability function of CPT is assumed to be a 2- parameter Weibull distribution:

$$P(CPT, \boldsymbol{\kappa}, \lambda) = 1 - e^{-(\mathrm{CPT}/\lambda)^{\boldsymbol{\kappa}}}$$

Given that a value of the mCPT represents the median or 50th percentile of the CPT and the value of P5MR represents the ratio of the 5%-tile of the CPT distribution to the mCPT, we can develop the following two equations to represent the cumulative distribution functions at the median CPT and the 5th percentile CPT:

$$P(mCPT, \kappa, \lambda) = 1 - e^{-\left(\frac{mCPT}{\lambda}\right)^{\kappa}} = 0.5 \quad (median)$$

$$P(P5MR \times mCPT, \kappa, \lambda) = 1 - e^{-\left(\frac{P5MR \times mCPT}{\lambda}\right)^{\kappa}} = 0.05 \quad (5th\ percentile)$$

Algebraically solving the equations above (see Appendix A for full derivation), we develop expressions for $\boldsymbol{\kappa}$ and λ:

$$\boldsymbol{\kappa} = \ln\left[\frac{\ln(0.95)}{\ln(0.5)}\right] / \ln(P5MR)$$

$$\lambda = e^{\frac{1}{\kappa} \times \ln\left[-\frac{mCPT^{\kappa}}{\ln(0.5)}\right]}$$

Table 1 below compares these two parameterizations for the example PDF and CDF distributions shown in Figures 1 and 2, respectively, for the $\boldsymbol{\kappa}$ and λ parameterizations shown there, illustrating the conversion to this new parameterization:

Table 1. Re-parameterization of Weibull Distribution Parameters from Traditional ($\boldsymbol{\kappa}$, λ) to Revised (P5MR, mCPT) for Example Weibull Distributions Appearing in Figures 1 and 2.

Parameterization Scheme				Description/Comments
Traditional		Revised		
Scale (λ) [a]	Shape (κ)	mCPT[b]	P5MR[c,d]	
1	0.5	0.480453	0.005476	- κ values of less than 1 indicate a failure rate decreases over time, and defective items fail early or are otherwise removed from the population.
1	1	0.693147	0.074001	- κ values equal to 1 indicate a constant failure rate over time possibly suggesting failure is due to random external events. - Here, the Weibull distribution reduces to the "exponential" distribution; - Note that mCPT here = 0.693 = ln(2)
1	1.5	0.78322	0.176261	- κ values greater than 1 suggests that the failure rate increases over time, as when there is an "aging" process or components are more likely to fail over time.
1	5	0.92932	0.594083	

[a] The Weibull scale parameter is the 63.2 percentile of the distribution. If the scale parameter is 1, then this means that 63.2% of the observed values will be smaller than 1. Note in the CDF in Figure 2, as a consequence, that all λ=1 distributions intersect at the 63.2 percentile.

[b] $mCPT = [\ln(2) * \exp(\boldsymbol{\kappa} * \ln(\lambda))]^{(1/\boldsymbol{\kappa})}$

[c] $P5MR = \exp(\ln(\ln(0.95)/\ln(0.5))/\boldsymbol{\kappa})$

[d] Note that as κ increases, the P5MR value becomes larger, indicating that the values at the 5th percentile approaches the values present at the 50th percentile, and the PDF becomes tighter and more peaked. K values of between 3 and 4 often lead to distributions that appear normal.

An example of the (varied) kinds of distributional "shapes" associated with various parameterizations is shown in Figure 2 as histograms of the CPT. More specifically, Figure 2 presents the CPT distributions with different medians and values of P5MR (ratio 5%-tile/mCPT). These present the CPT distributions with different mCPTs (2-, 4-, 6-, and 8-hrs) and values of

the P5MR ratio (P5MR= 0.2, 0.3, 0.4, and 0.6) for the (assumed) Weibull Distribution[11]. As seen in Figure 2, larger mCPTs are associated with a shift in the distribution toward the right. In addition -- and importantly -- smaller P5MR values in this range are associated with "flatter" distributions and larger P5MRs are associated with more "peaked" distributions, with these more peaked distributions showing a greater percentage of the distribution centered around the median. From a regulatory perspective, a CPT distribution with a larger P5MR is more desirable than a CPT distribution with smaller P5MR since this means that a greater percentage of the user population experiences an actual CPT closer to the (advertised) mCPT. Further, it could be argued from a public policy perspective that a large variability in CPT in the population for a given repellent is not a desirable characteristic and does not accurately portray or indicate any "expected" mCPT on the part of the consumer.

OPP staff have judged what might be considered reasonable values for input parameters (*precision* of the estimated mCPT and *variability* in CPT in (or among) users of the tested product) in order to estimate required number of test subjects for the field exercise to achieve a desired set of aims regarding precision around the estimate of the mCPT. These judgments are based in part on available data and past experiences[12] and in part on general thoughts regarding consumer expectations with respect to product efficacy. Specifically, EPA has estimated the power associated with various sample sizes where power -- as defined here – is the probability that the ratio of the (95% LCL_{mCPT})/(estimated mCPT) is greater than a given acceptable K (a scalar which measures the precision of the estimates in estimating the mCPT). Such mosquito repellency study design power depends on:

- Number of test subjects
    - The larger the number of test subjects, the greater the power

- (The required) precision (K) for estimated mCPT
    - The precision of an estimated mCPT from a study is expressed by the value of the ratio 95% LCL_{mCPT}/estimated mCPT. The value of ratio is in the interval (0, 1).
    - K is the smallest acceptable value of the ratio 95% LCL_{mCPT}/estimated mCPT for a given trial to be considered a "success", and conceptually represents an inverse of precision ("tightness") in the estimate of the mCPT: a larger K represents a greater "tightness" around the estimated mCPT. As K is chosen to be smaller, there is a greater probability that ratio 95% LCL_{mCPT}/estimated mCPT > K (and the trial is considered to be a "success" in the power calculation)

[11]Other simulations were performed for the lognormal, normal, and uniform distributions, with the latter one (particularly) done as a form of sensitivity analysis but these are not discussed in this report; the simulation outputs, however, are provided in Appendix D. Note that the power estimates for a given sample size from the Weibull and Lognormal distributions are similar.

[12]See Appendix B for Weibull parameters fit to previous mosquito efficacy field data that the EPA has evaluated for a similar design and experimental set-up. In general, the values found in these (prior) studies support the values selected here to be used for the simulation

- P5MR
    - P5MR = ratio of the 5th percentile/mCPT
    - As the variation (dispersion or spread) of the distribution of CPT in the population becomes smaller, the 95% confidence interval of the estimated mCPT also becomes narrower (i.e., the 95% LCL_{mCPT} is closer to the estimated mCPT and the mCPT is better estimated, *certeris paribus*). Therefore, a smaller variation in the distribution of CPT will result in a larger P5MR and a higher probability that the ratio 95% LCL_{mCPT}/estimated mCPT > K. A CPT distribution with greater P5MR is generally more desirable than a CPT distribution with smaller P5MR

Ideally, a mosquito repellency study will be designed to have a sufficient number of test subjects such that one can have reasonable assurance that there is adequate power (defined here as a high probability that the ratio 95% LCL/estimated mCPT > K) given a shape and spread of the CPT distribution in the population. This shape/spread of the CPT in the population is defined by the P5MR.

Brief Description of the Conduct of a Field Mosquitoes Repellent Study

In mosquito field repellency studies, test subjects are exposed in the field for 5-minute intervals immediately following product application and then for 5 minutes every 30 minutes until a "first confirmed landing" occurs. For subjects who receive confirmed landings, the CPTs are set as 0 if the first confirmed landing occurs during the first 5 minutes after application of the repellent; otherwise, the CPTs are rounded down to the nearest half hour (i.e., the starting time of the exposure period in which the first confirmed landing occurs). For those subjects for which there are no confirmed landings through the end of the testing day, CPTs are considered to be right censored at a time that is rounded down to the nearest half hour.

Description of (Computer) Simulation Procedure:

To simulate the field study trials, 4000 datasets were created with each dataset consisting of 10 data points (representing CPTs of 10 subjects) that were generated randomly from a Weibull distribution with a median CPT=2 and ratio of the 5%-tile/median P5MR= 0.2. If the randomly generated CPTs for the 10 subjects are ≤ 5, 6-35, 36-65, 66-95, … 576-605 minutes, the CPTs are set to be 0-, 0.5-, 1-, 1.5 hours…10 hours, respectively, to simulate the study design in which each study participant is exposed for 5 of every 30 minutes until the first confirmed mosquito landing. If the randomly generated CPTs are greater than 10 hours (or 605 minutes), they are considered in the calculation to be (right) censored at 10 hours.

After generating the CPTs as described in the previous paragraph, the Kaplan Meier Estimator is used to estimate the mCPT and its 95% CI for each of the 4000 (10-person) datasets. The proportion of datasets in which the ratio of 95% LCL_{mCPT}/mCPT > K as 0.6 is considered to be the "power" of the study design. More specifically: if the value of 95% LCL/mCPT >0.6 is considered a "success", the power is calculated as the proportion of successes in the 4000 datasets consisting of 10 data points each.

The process described in previous paragraph is then repeated for each combination of different mCPT = 2, 4, 6, and 8 hours; P5MR = 0.2, 0.4, 0.5, 0.6, 0.7, and 0.8; sample size per dataset = 10, 11, 12 … 20; and the lowest acceptable K = 0.6, 0.7, and 0.8; all assuming that CPT follows a Weibull distribution[13].

[13] Such calculations were similarly done for the lognormal distribution, normal distribution, and uniform distribution, but are not discussed further in this report. The SAS output from these calculations and various associated tables and graphs, however, is shown in Appendix D for completeness.

Results of Simulation

Tables 2, 3, and 4 present the power estimates from simulations in which the data were randomly generated from Weibull distributions for K = 0.6, 0.7, and 0.8, respectively. These are shown for various values of mCPT (ranging from 2 to 8 hours), P5MR (ranging from 0.2 to 0.8), and Sample Size (ranging from 10 to 20). As described earlier, K reflects a measure the precision of the estimate of mCPT with larger K values representing tighter estimates. For example, the K value of 0.6 requires that the 95% LCL on a median protection of 10 hours be no less than 6 hours (for a "success") while a K value of 0.8 requires that the 95% LCL on that same median protection time be no less than 8 hours. A required precision of a K of 0.8, then, requires a more precise estimate of the mCPT than a K of 0.6 for this trial to be considered a "success" in the power calculation.

Figures 4, 5, and 6 present visually the same results in Tables 2, 3, and 4 (as power curves rather than tables).

As can be seen within each Table or Figure, the power of a study to achieve a given acceptable ratio K value (e.g., 0.6, 0.7, or 0.8 representing 95% LCL_{mCPT}/mCPT) value increases as the assumed P5MR value of the distribution increases (for example, from 0.2 to 0.8) or as the sample size increases (from 10 to 20). This is expected since a tighter (or more "peaked") distributions (as evidenced by a larger P5MR value) will require fewer random "draws" to accurately estimate the mCPT. Across the Figures or Tables, we also see that as the acceptable K value increases from 0.6 to 0.8, the power of a study to achieve "95% LCL_{mCPT}/mCPT > K" decreases since stricter requirements for a "success" are being levied.

The SAS Code used to generate the simulated data and the associated tables and graphs are presented in Appendix C. Note - as described earlier - those simulations were also performed for the lognormal, normal, and uniform distributions, in part to serve as a sensitivity analysis and these are presented in the Appendix D for completeness but are not discussed further here.

Figure 1. Probability Density Function (PDF) for Weibull Plot with λ (scale) =1 and κ (shape) ranging from 0.5 to 5.

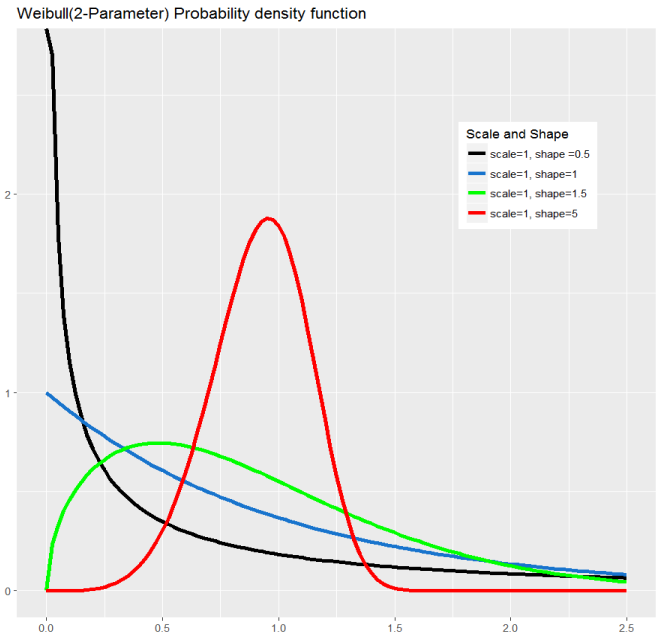


Figure 2. Cumulative Distribution Function (CDF) for Above Weibull PDF.

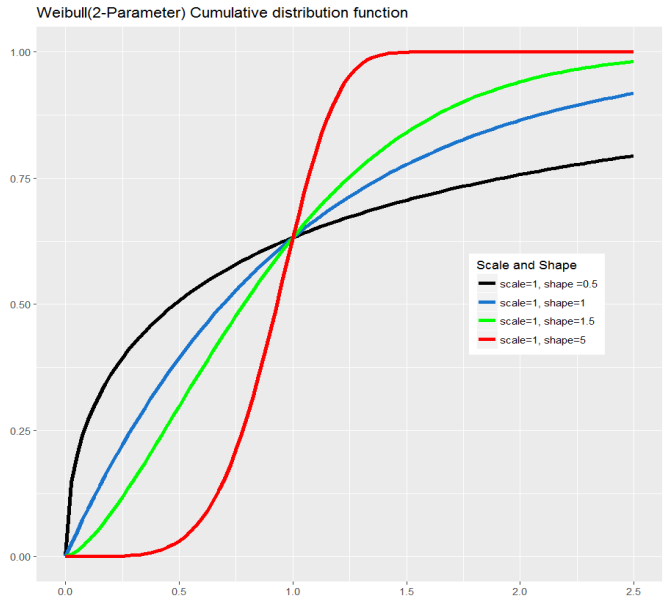


Figure 3: Histograms of CPT distributions for various CPTs and P5MRs (assume CPTs are Weibull distributions).

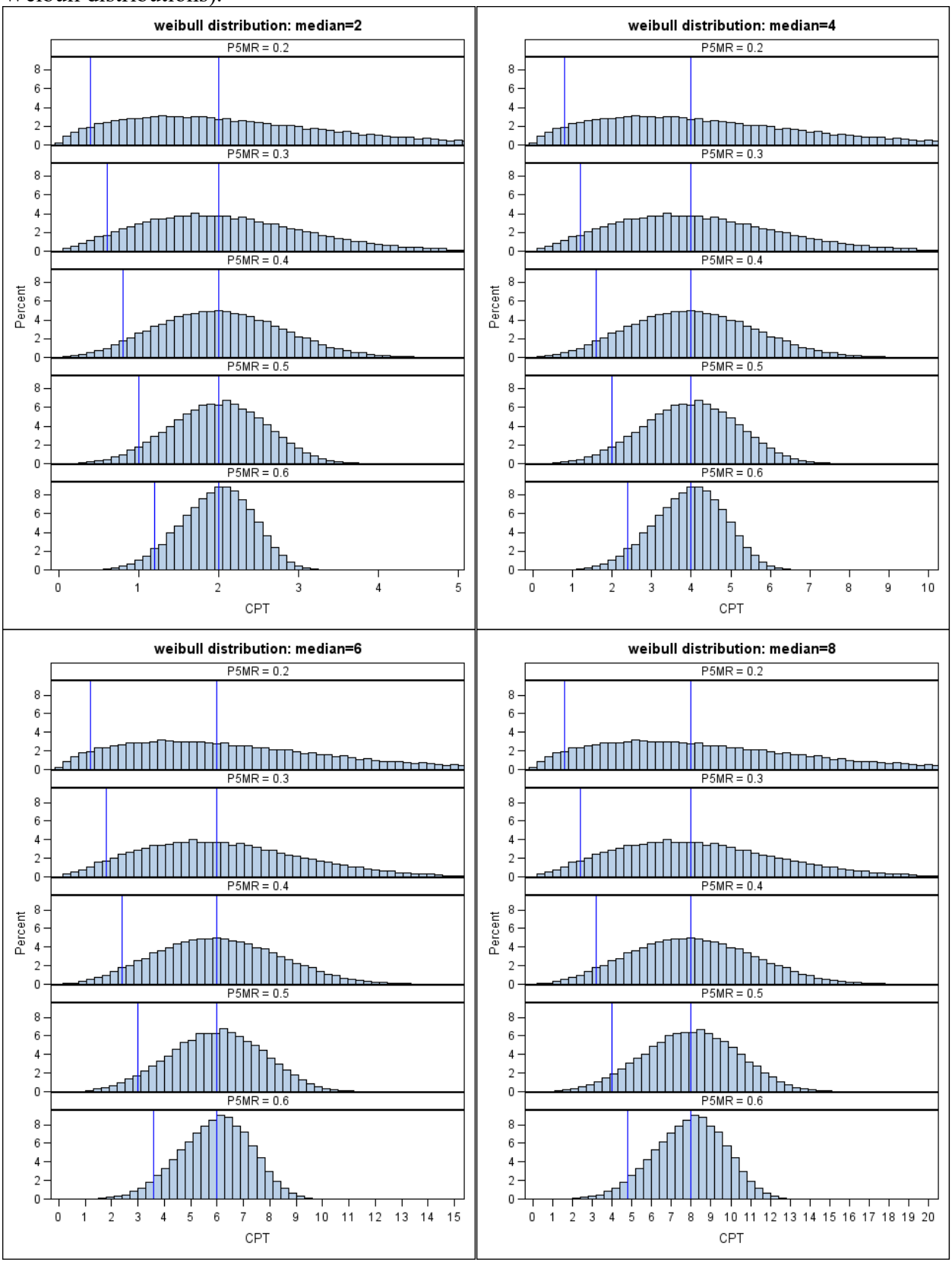


Table 2: Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.6 (Weibull distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.071	0.291	0.207	0.473	0.362	0.369	0.502	0.494	0.637	0.626	0.521
	0.4	0.297	0.691	0.594	0.841	0.804	0.779	0.893	0.898	0.939	0.945	0.932
	0.5	0.498	0.850	0.802	0.942	0.938	0.921	0.968	0.977	0.964	0.982	0.986
	0.6	0.733	0.949	0.943	0.962	0.971	0.955	0.954	0.979	0.915	0.951	0.971
	0.7	0.893	0.945	0.955	0.875	0.918	0.852	0.855	0.893	0.810	0.859	0.886
	0.8	0.819	0.786	0.826	0.666	0.734	0.591	0.637	0.708	0.558	0.632	0.689
4	0.2	0.043	0.208	0.146	0.356	0.289	0.254	0.432	0.380	0.567	0.516	0.435
	0.4	0.241	0.595	0.521	0.783	0.737	0.709	0.849	0.842	0.930	0.920	0.884
	0.5	0.412	0.795	0.730	0.921	0.901	0.888	0.956	0.964	0.986	0.988	0.973
	0.6	0.648	0.938	0.899	0.987	0.980	0.976	0.995	0.997	0.997	0.999	0.998
	0.7	0.869	0.988	0.986	0.993	0.995	0.994	0.992	0.998	0.977	0.992	0.996
	0.8	0.975	0.982	0.987	0.948	0.970	0.949	0.934	0.968	0.887	0.932	0.954
6	0.2	0.075	0.204	0.153	0.339	0.280	0.252	0.426	0.369	0.557	0.490	0.424
	0.4	0.227	0.572	0.504	0.759	0.743	0.689	0.851	0.826	0.929	0.916	0.885
	0.5	0.408	0.779	0.729	0.914	0.905	0.873	0.963	0.958	0.987	0.981	0.978
	0.6	0.645	0.925	0.906	0.984	0.980	0.977	0.997	0.997	1.000	0.999	0.999
	0.7	0.874	0.990	0.988	0.998	0.999	0.999	1.000	1.000	0.999	1.000	1.000
	0.8	0.986	0.998	0.999	0.993	0.995	0.994	0.990	0.997	0.975	0.989	0.995
8	0.2	0.323	0.346	0.362	0.457	0.443	0.361	0.537	0.453	0.636	0.564	0.522
	0.4	0.314	0.586	0.552	0.769	0.753	0.700	0.858	0.836	0.934	0.919	0.891
	0.5	0.421	0.779	0.732	0.914	0.904	0.875	0.960	0.956	0.989	0.985	0.979
	0.6	0.638	0.927	0.906	0.983	0.979	0.974	0.997	0.997	1.000	0.999	1.000
	0.7	0.874	0.990	0.989	0.999	1.000	0.999	1.000	1.000	1.000	1.000	1.000
	0.8	0.985	0.999	1.000	0.997	1.000	0.999	0.998	1.000	0.994	0.998	0.999

NOTE: Yellow indicates power > 0.8; orange indicates power > 0.9; blue indicates unusual power when median complete protection time = 2 hours and P5MR = 0.8.

Table 3: Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.7 (Weibull distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.022	0.096	0.066	0.199	0.121	0.128	0.217	0.211	0.304	0.299	0.222
	0.4	0.132	0.415	0.299	0.607	0.484	0.522	0.634	0.677	0.751	0.767	0.668
	0.5	0.267	0.633	0.516	0.789	0.697	0.748	0.803	0.851	0.868	0.895	0.838
	0.6	0.476	0.813	0.732	0.881	0.845	0.864	0.885	0.919	0.893	0.926	0.918
	0.7	0.694	0.895	0.876	0.861	0.889	0.847	0.850	0.888	0.799	0.837	0.888
	0.8	0.768	0.780	0.821	0.673	0.750	0.591	0.652	0.699	0.566	0.622	0.694
4	0.2	0.016	0.075	0.053	0.166	0.109	0.088	0.190	0.171	0.276	0.245	0.177
	0.4	0.103	0.332	0.267	0.517	0.452	0.402	0.620	0.555	0.752	0.681	0.638
	0.5	0.210	0.525	0.468	0.715	0.685	0.624	0.830	0.776	0.914	0.866	0.848
	0.6	0.402	0.736	0.714	0.886	0.880	0.833	0.955	0.923	0.979	0.966	0.969
	0.7	0.673	0.914	0.917	0.971	0.975	0.962	0.987	0.986	0.982	0.988	0.995
	0.8	0.927	0.970	0.987	0.945	0.971	0.946	0.931	0.955	0.892	0.922	0.958
6	0.2	0.047	0.083	0.066	0.158	0.105	0.083	0.174	0.150	0.247	0.218	0.149
	0.4	0.079	0.294	0.225	0.473	0.387	0.356	0.556	0.507	0.690	0.636	0.566
	0.5	0.172	0.483	0.406	0.679	0.622	0.573	0.779	0.735	0.887	0.841	0.806
	0.6	0.335	0.697	0.649	0.861	0.851	0.804	0.938	0.909	0.977	0.963	0.956
	0.7	0.607	0.894	0.885	0.975	0.970	0.958	0.994	0.989	0.997	0.996	0.997
	0.8	0.897	0.987	0.992	0.988	0.995	0.993	0.989	0.993	0.978	0.987	0.995
8	0.2	0.309	0.234	0.297	0.289	0.320	0.210	0.347	0.251	0.392	0.306	0.306
	0.4	0.180	0.321	0.294	0.497	0.435	0.379	0.598	0.521	0.726	0.654	0.592
	0.5	0.206	0.499	0.439	0.692	0.645	0.603	0.804	0.762	0.904	0.867	0.830
	0.6	0.357	0.731	0.684	0.892	0.872	0.831	0.957	0.933	0.983	0.978	0.966
	0.7	0.634	0.922	0.907	0.985	0.981	0.976	0.998	0.994	0.998	0.998	0.999
	0.8	0.913	0.996	0.995	0.999	0.999	0.998	0.997	1.000	0.994	0.997	0.999

NOTE: Yellow indicates power > 0.8; orange indicates power > 0.9; blue indicates unusual power when median complete protection time = 2 hours and P5MR = 0.8.

Table 4: Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.8 (Weibull distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.007	0.032	0.027	0.064	0.044	0.027	0.079	0.061	0.115	0.088	0.071
	0.4	0.035	0.119	0.103	0.219	0.188	0.140	0.275	0.227	0.355	0.287	0.258
	0.5	0.068	0.210	0.185	0.339	0.297	0.251	0.418	0.364	0.506	0.460	0.425
	0.6	0.133	0.341	0.306	0.496	0.473	0.407	0.594	0.560	0.678	0.670	0.641
	0.7	0.251	0.561	0.532	0.679	0.692	0.598	0.753	0.753	0.749	0.775	0.809
	0.8	0.455	0.696	0.728	0.654	0.728	0.562	0.648	0.694	0.565	0.620	0.692
4	0.2	0.004	0.026	0.012	0.053	0.027	0.022	0.054	0.045	0.085	0.065	0.042
	0.4	0.026	0.093	0.080	0.186	0.151	0.103	0.254	0.182	0.346	0.245	0.228
	0.5	0.060	0.170	0.165	0.315	0.297	0.202	0.436	0.315	0.546	0.413	0.414
	0.6	0.135	0.317	0.320	0.494	0.499	0.374	0.650	0.529	0.760	0.643	0.639
	0.7	0.295	0.548	0.565	0.726	0.754	0.651	0.863	0.784	0.914	0.854	0.873
	0.8	0.619	0.828	0.867	0.884	0.923	0.864	0.913	0.922	0.886	0.909	0.947
6	0.2	0.038	0.033	0.027	0.055	0.037	0.027	0.053	0.033	0.076	0.058	0.039
	0.4	0.022	0.098	0.072	0.206	0.135	0.115	0.234	0.196	0.341	0.289	0.214
	0.5	0.054	0.205	0.154	0.364	0.281	0.248	0.438	0.382	0.567	0.493	0.425
	0.6	0.133	0.383	0.335	0.572	0.525	0.473	0.694	0.626	0.812	0.748	0.716
	0.7	0.316	0.646	0.614	0.819	0.818	0.750	0.918	0.874	0.965	0.943	0.938
	0.8	0.670	0.916	0.917	0.967	0.974	0.962	0.986	0.984	0.977	0.985	0.993
8	0.2	0.301	0.193	0.270	0.198	0.264	0.155	0.250	0.157	0.244	0.171	0.206
	0.4	0.122	0.136	0.141	0.227	0.182	0.142	0.267	0.208	0.340	0.292	0.229
	0.5	0.082	0.209	0.165	0.368	0.282	0.256	0.434	0.392	0.561	0.505	0.424
	0.6	0.124	0.390	0.321	0.588	0.514	0.490	0.688	0.655	0.823	0.779	0.710
	0.7	0.299	0.683	0.610	0.857	0.808	0.794	0.915	0.909	0.966	0.963	0.939
	0.8	0.644	0.940	0.909	0.989	0.978	0.981	0.994	0.995	0.993	0.995	0.998

NOTE: Yellow indicates power > 0.8; orange indicates power > 0.9.

Figure 4: Power curves of study design when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.6 (Weibull distributions).

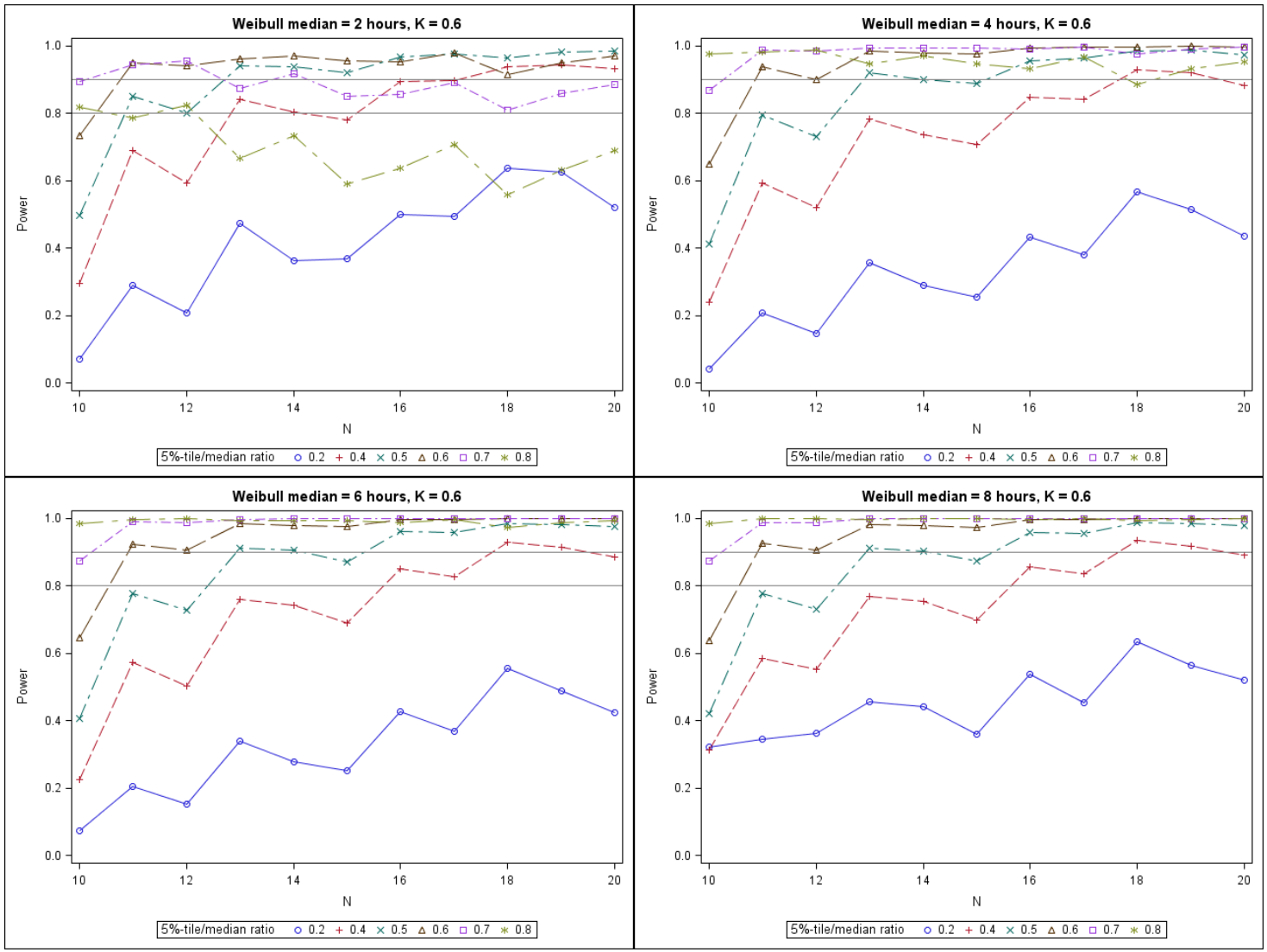


Figure 5: Power curves of study design when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.7 (Weibull distributions).

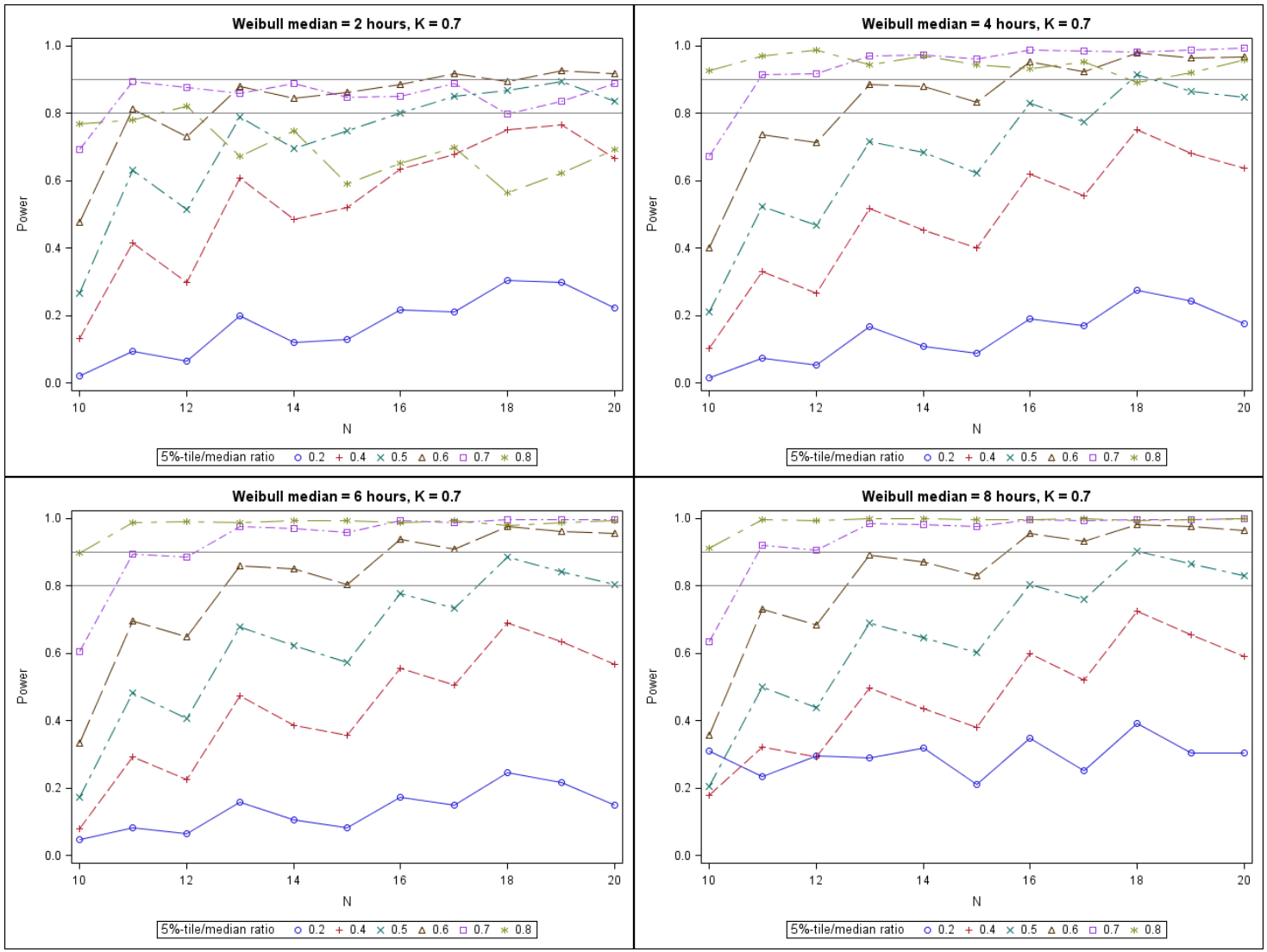
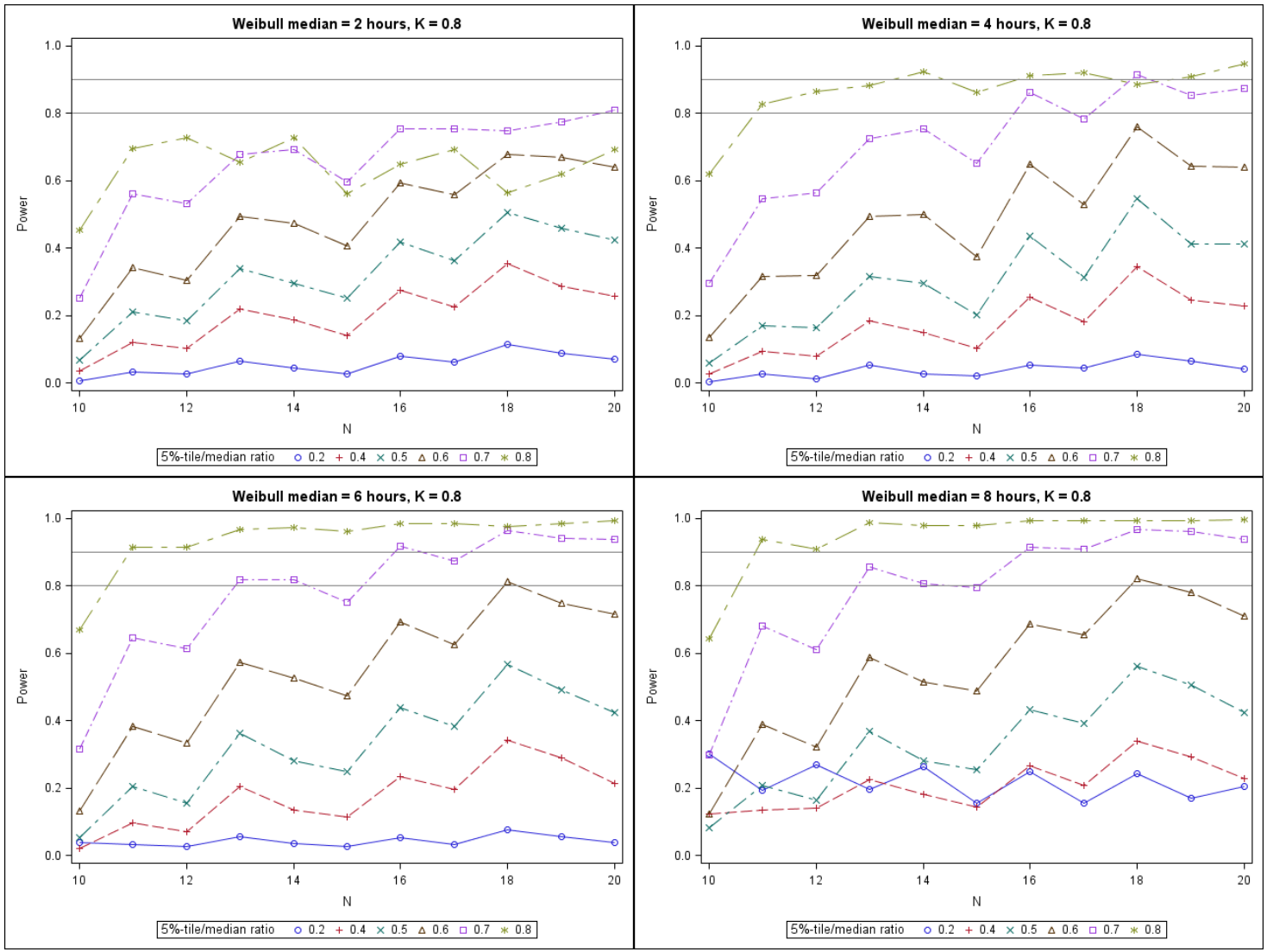


Figure 6: Power curves of study design when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.8 (Weibull distributions).



APPENDIX A

Re-parameterization of Standard Weibull Equation

Given the definition of PDF and CDF from first principles:

$$P(mCPT, \kappa, \lambda) = 1 - e^{-\left(\frac{mCPT}{\lambda}\right)^{\kappa}} = 0.5 \quad (median)$$
$$P(P5MR \times mCPT, \kappa, \lambda) = 1 - e^{-\left(\frac{P5MR \times mCPT}{\lambda}\right)^{\kappa}} = 0.05 \quad (5th\ percentile)$$

Then:

$$e^{-\left(\frac{mCPT}{\lambda}\right)^{\kappa}} = 0.5 \quad (median)$$
$$e^{-\left(\frac{P5MR \times mCPT}{\lambda}\right)^{\kappa}} = 0.95 \quad (5th\ percentile)$$

and

$$-\left(\frac{\mathrm{mCPT}}{\lambda}\right)^{\kappa} = \ln(0.5) \qquad (1)$$
$$-\left(\frac{\mathrm{P5MR \times mCPT}}{\lambda}\right)^{\kappa} = \ln(0.95) \qquad (2)$$

Divide (2) by (1), we have:

$$\left[\frac{\frac{P5MR \times mCPT}{\lambda}}{\frac{mCPT}{\lambda}}\right]^{\kappa} = \frac{\ln(0.95)}{\ln(0.5)}$$

$$\kappa = \ln\left[\frac{\ln(0.95)}{\ln(0.5)}\right] / \ln(P5MR) \qquad (3)$$

From (1):

$$\left(\frac{mCPT}{\lambda}\right)^{\kappa} = -\ln(0.5)$$

$$\kappa \times ln\left(\frac{mCPT}{\lambda}\right) = \ln[-\ln(0.5)]$$

$$\ln\left(\frac{mCPT}{\lambda}\right) = \frac{1}{\kappa} \ln[-\ln(0.5)]$$

$$\ln(mCPT) - \ln(\lambda) = \frac{1}{\kappa} \ln[-\ln(0.5)]$$
$$\ln(\lambda) = \ln(mCPT) - \frac{1}{\kappa} \ln[-\ln(0.5)]$$
$$= \frac{1}{\kappa} [\kappa \ln(mCPT) - \ln[-\ln(0.5)]]$$

$$= \frac{1}{\kappa}\left[\ln(mCPT^{\kappa}) - \ln[-\ln(0.5)]\right]$$

$$= \frac{1}{\kappa}\ln\left[-\frac{mCPT^{\kappa}}{\ln(0.5)}\right]$$

$$\lambda = e^{\frac{1}{\kappa}\ln\left[-\frac{mCPT^{\kappa}}{\ln(0.5)}\right]} \qquad (4)$$

So…

$$\kappa = \ln\left[\frac{\ln(0.95)}{\ln(0.5)}\right] / \ln(P5MR)$$

$$\lambda = e^{\frac{1}{\kappa}\times\ln\left[-\frac{mCPT^{\kappa}}{\ln(0.5)}\right]}$$

(As shown in the main text)

APPENDIX B

Product	Location	Sample size	Est. mCPT (95% CI)	Ratio of 95% LCL/est. mCPT	Est. Weibull (shape κ; scale λ)	Est. P5MR
A	1	10	7.5 (4.0, 8.0)	0.53	6.602; 7.777	0.674
	2	10	8.5 (4.5, 10.0)	0.53	5.855; 8.624	0.641
B	1	10	12.0 (6.0, 12.0)	0.50	4.311; 10.669	0.547
	2	10	12.0 (8.5, 12.0)	0.71	10.424; 11.516	0.779
C	1	10	7.5 (4.0, 9.0)	0.53	4.430; 8.146	0.556
	2	8	5.0 (2.5, 5.5)	0.50	5.318; 4.915	0.613
D	1	10	2.0 (1.5, 2.0)	0.75	7.004; 2.135	0.690
	2	10	2.5 (1.0, 3.5)	0.40	3.557; 2.8970	0.481
E	1	10	8.25 (6.0, 10.0)	0.73	7.609; 8.733	0.710
	2	10	8.0 (3.5, 8.5)	0.44	4.009; 7.442	0.522

APPENDIX C

SAS codes

```
*============================================================*
* Programmer: James Nguyen, USEPA                            *
*                                                            *
* Project: Mosquito Repellency Studies                       *
*                                                            *
* Purpose: Power Analysis/sample size calculation            *
*                                                            *
* Description:                                               *
*     - distributions: Weibull, Normal, Lognormal, Uniform   *
*     - create histograms of the distributions               *
*     - SAS Procedures: PROC LIFETEST and PROC ICLIFETEST    *
*                                                            *
* Review Date: 4/10/2017                                          *
*============================================================*;
options formdlim="=" ps=90 ls=90 nonumber nodate;

libname MOS "C:\Users\JNguyen\Desktop\MOS";

%Macro distParam;
        if upcase(Distribution) = "WEIBULL" then do;
                * Weibull = f(x,a,b);
                a = log(log(0.95)/log(0.5))/log(P5MR);              b = exp((1/a)*log(-
(MED**a)/log(0.5)));
        end;
        if upcase(Distribution) = "UNIFORM" then do;
                * uniform = U[a, b];
                a = MED*(0.5*P5MR - 0.05)/0.45;             b = MED*2 - a;
        end;
        if upcase(Distribution) = "NORMAL" then do;
                *normal = N(a,b);
                a = MED;               b = MED*(1-P5MR)/1.645;
        end;
        if upcase(Distribution) = "LOGNORMAL" then do;
                * lognormal = exp(N(a,b));
                a = log(MED);          b = (log(MED)-log(MED*P5MR))/1.645;
        end;
%Mend;title;

%Macro generate;
        if upcase(Distribution) = "WEIBULL"   then CPT = rand("Weibull", a, b);
        if upcase(Distribution) = "LOGNORMAL" then CPT = exp(rand("Normal", a, b));
        if upcase(Distribution) = "NORMAL"           then CPT = rand("Normal", a, b);
        if upcase(Distribution) = "UNIFORM"          then CPT = a + (b-a)*rand("Uniform");
%Mend;

%Macro Histogram(MED=, P5MRS=, dist=, seed=);

        %let N=1;
        %let P5MR&N = %nrbquote(%scan(&P5MRS,&N, %str( )));
        %do %while (&&P5MR&N ^=);
                %let N=%eval(&N+1);
                %let P5MR&N = %nrbquote(%scan(&P5MRS,&N, %str( )));
        %end;
        %let N=%eval(&N-1);


        Data Parameters;
                MED = &MED;
                %do i = 1 %to &N;
                        P5MR = &&P5MR&i;
                        P5 = MED*P5MR;
                        output;
```

```
		%end;
		label MED = "P50";
	run;

	Data Parameters;
		set Parameters;
		Distribution = "&dist";
		%distParam;
	run;

	data simmer;
		call streaminit(&seed);
		set parameters;
		do i = 1 to 50000;
			%generate;
			output;
		end; *i;
		drop i a b;
	run;

	title "&dist distribution: median=&MED";
	Proc SGPANEL data = Simmer;
		panelby P5MR/rows=&N;
		Histogram CPT/binwidth=%sysevalf(2.5*&MED/50);
		refline P5 /axis=x lineattrs=(pattern=1 thickness=1 color=blue);
		refline MED/axis=x lineattrs=(pattern=1 thickness=1 color=blue);
		colaxis values = (0 to %sysevalf(2.5*&MED) by 1);
	run;
	Proc datasets nolist; save sasmacr; run;quit;
%Mend;title;

%Histogram(MED=2,  P5MRS=0.2 0.3 0.4 0.5 0.6, dist=weibull, seed=279420);
%Histogram(MED=4,  P5MRS=0.2 0.3 0.4 0.5 0.6, dist=weibull, seed=279420);
%Histogram(MED=6,  P5MRS=0.2 0.3 0.4 0.5 0.6, dist=weibull, seed=279420);
%Histogram(MED=8,  P5MRS=0.2 0.3 0.4 0.5 0.6, dist=weibull, seed=279420);
%Histogram(MED=10, P5MRS=0.2 0.3 0.4 0.5 0.6, dist=weibull, seed=279420);



%Macro Histogram1(MED=, P5MR=, seed=);

	Data Parameters;
		MED = &MED;
		P5MR = &P5MR;
		P5 = MED*P5MR;

		do i = 1 to 4;
			if i = 1 then Distribution = "Lognormal";
			if i = 2 then Distribution = "Normal";
			if i = 3 then Distribution = "Uniform";
			if i = 4 then Distribution = "Weibull";
			%distParam;
			output;
		end;
		label MED = "P50" P5MR="5%-tile/median"; drop i;
	run;

	data simmer;
		call streaminit(&seed);
		set parameters;
		do i = 1 to 50000;
			%generate;
			output;
		end; *i;
		drop i a b;
	run;

	title "median=&MED    P5MR=&P5MR" ;
	Proc SGPANEL data = Simmer;
		panelby Distribution/rows=4;
```

```
                Histogram CPT/binwidth=%sysevalf(2.5*&MED/50);
                refline P5 /axis=x lineattrs=(pattern=1 thickness=1 color=blue);
                refline MED/axis=x lineattrs=(pattern=1 thickness=1 color=blue);
                colaxis values = (0 to %sysevalf(2.5*&MED) by 1);
        run;
        Proc datasets nolist; save sasmacr; run;quit;
%Mend;title;

%Histogram1(MED=2,  P5MR=0.2, seed=279420);
%Histogram1(MED=2,  P5MR=0.4, seed=279420);
%Histogram1(MED=2,  P5MR=0.5, seed=279420);
%Histogram1(MED=2,  P5MR=0.6, seed=279420);
%Histogram1(MED=2,  P5MR=0.7, seed=279420);



%Macro CPT;
        CPT=CPT*60;
        if CPT <= 5 then do;
                LT = 0;                RT = 0;   CPT= 0;             censor = 0;
        end;
        else if CPT >= &maxT*60 then do;
                LT = &maxT*60; RT=.;   CPT=&maxT*60;  censor = 1;
        end;
        else do;
                LT = 30*floor((CPT-5)/30)+5; RT = 30*ceil((CPT-5)/30);      CPT = RT;
        censor = 0;
        end;

        CPT = CPT/60;
        LT = LT/60;
        RT = RT/60;
%Mend;title;


%Macro power;
        ods select none;
        %if &censor=right %then %do;
                ods output Quartiles=MPT;
                Proc lifetest data = Simmer(keep=MED P5MR N Sim CPT Censor);
                        by MED P5MR N Sim;
                        time CPT*Censor(1);
                run;
        %end;
        %if &censor=interval %then %do;
                ods output quartiles=MPT;
                Proc iclifetest data = simmer(keep=MED P5MR N Sim LT RT) method=turnbull
impute(seed=1234);
                        by MED P5MR N Sim;
                        time (LT, RT);
                run;
        %end;
        ods select default;

        Proc datasets nolist; delete simmer; run;quit;

        Data MPT;
                set MPT;
                if percent = 50;
                power = (LowerLimit >= &K*Estimate);
                %if &censor=right %then %do; Censor = "right";%end;
                %if &censor=interval %then %do; Censor = "interval"; %end;
        run;

        Proc SQL;
                create table &dist&MED as
                select Censor, MED, P5MR, N, avg(Power) as Power
                from MPT
                group by Censor, MED, P5MR, N;
        quit;
```

```
%Mend;title;
%Macro Mosquito(med=, P5MRS=, nmin=,nmax=,maxT=,K=,dist=,censor=,NSim=, seed=);

	%let N=1;
	%let P5MR&N = %nrbquote(%scan(&P5MRS,&N, %str( )));
	%do %while (&&P5MR&N ^=);
		%let N=%eval(&N+1);
		%let P5MR&N = %nrbquote(%scan(&P5MRS,&N, %str( )));
	%end;
	%let N=%eval(&N-1);


	%do i = 1 %to &N;

		%if &i = 1 %then %do; data All_&dist&MED; set _NULL_; run; %end;

		Data Parameters;
			MED = &MED;
			P5MR = &&P5MR&i;
			P5 = MED*P5MR;
			label MED = "median" P5MR="5%-tile/median ratio";
		run;

		Data Parameters;
			set Parameters;
			Distribution = "&dist";
			%distParam;
		run;

		data simmer;
			call streaminit(&seed);
			set Parameters;
			do N = &Nmin to &Nmax;
				do Sim = 1 to &NSim;
					do ID = 1 to N;
						%generate;
						output;
					end; *ID;
				end; *Sim;
			end; *N;
			drop a b;
		run;

		Data Simmer;
			set Simmer;
			%CPT;
		run;

		%power;

		Data All_&dist&MED;
			set All_&dist&MED &dist&MED;
		run;

		Proc datasets nolist; delete Parameters simmer MPT &dist&MED; quit;

	%end;

	Data MOS.&dist._&censor._MED&MED._K%sysevalf(100*&K);
		set All_&dist&MED;
	run;

	Proc datasets nolist; save sasmacr; run;quit;

%Mend;


dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= weibull, censor=right, NSim=4000, seed=561);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= weibull, censor=right, NSim=4000, seed=561);
```

```
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= weibull, censor=right, NSim=4000, seed=561);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= weibull, censor=right, NSim=4000, seed=561);

dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= weibull, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= weibull, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= weibull, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= weibull, censor=right, NSim=4000, seed=352);

dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= weibull, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= weibull, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= weibull, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= weibull, censor=right, NSim=4000, seed=352);


dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Lognormal, censor=right, NSim=4000, seed=561);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Lognormal, censor=right, NSim=4000, seed=561);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Lognormal, censor=right, NSim=4000, seed=561);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Lognormal, censor=right, NSim=4000, seed=561);

dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Lognormal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Lognormal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Lognormal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Lognormal, censor=right, NSim=4000, seed=352);

dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Lognormal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Lognormal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Lognormal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Lognormal, censor=right, NSim=4000, seed=352);


dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Normal, censor=right, NSim=4000, seed=561);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Normal, censor=right, NSim=4000, seed=561);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Normal, censor=right, NSim=4000, seed=561);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Normal, censor=right, NSim=4000, seed=561);

dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Normal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Normal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Normal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Normal, censor=right, NSim=4000, seed=352);
```

```
dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Normal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Normal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Normal, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Normal, censor=right, NSim=4000, seed=352);


dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Uniform, censor=right, NSim=4000, seed=561);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Uniform, censor=right, NSim=4000, seed=561);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Uniform, censor=right, NSim=4000, seed=561);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.6, dist= Uniform, censor=right, NSim=4000, seed=561);

dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Uniform, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Uniform, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Uniform, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Uniform, censor=right, NSim=4000, seed=352);

dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Uniform, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Uniform, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Uniform, censor=right, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.8, dist= Uniform, censor=right, NSim=4000, seed=352);


/*
dm log 'clear';%Mosquito(med=2, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Weibull, censor=interval, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=4, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Weibull, censor=interval, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=6, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Weibull, censor=interval, NSim=4000, seed=352);
dm log 'clear';%Mosquito(med=8, P5MRS=0.2 0.4 0.5 0.6 0.7 0.8, nmin=10, nmax=20, maxT=10,
K = 0.7, dist= Weibull, censor=interval, NSim=4000, seed=352);
*/



*=====> Create Figures and Print Results;


libname MOS "C:\Users\JNguyen\Desktop\MOS";
%let folder=C:\Users\JNguyen\Desktop\MOS;

%Macro SGPLOT(distribution=, K=);
        title "&distribution median = 2 hours, K = 0.&K";
        Proc SGPLOT data = MOS.&distribution._right_med2_k&k.0;
                scatter x = N y = Power/group = P5MR;
                series x = N y = Power/group = P5MR;
                refline 0.8 0.9/axis=y;
                yaxis min=0 max=1;
        run;
        title "&distribution median = 4 hours, K = 0.&K";
        Proc SGPLOT data = MOS.&distribution._right_med4_k&k.0;
                scatter x = N y = Power/group = P5MR;
                series x = N y = Power/group = P5MR;
                refline 0.8 0.9/axis=y;
```

```
                yaxis min=0 max=1;
        run;
        title "&distribution median = 6 hours, K = 0.&K";
        Proc SGPLOT data = MOS.&distribution._right_med6_k&k.0;
                scatter x = N y = Power/group = P5MR;
                series x = N y = Power/group = P5MR;
                refline 0.8 0.9/axis=y;
                yaxis min=0 max=1;
        run;
        title "&distribution median = 8 hours, K = 0.&K";
        Proc SGPLOT data = MOS.&distribution._right_med8_k&k.0;
                scatter x = N y = Power/group = P5MR;
                series x = N y = Power/group = P5MR;
                refline 0.8 0.9/axis=y;
                yaxis min=0 max=1;
        run;
%Mend;

%Macro print(distribution=, K=);
        data &distribution._K&K;
                set MOS.&distribution._right_med2_k&k.0
                        MOS.&distribution._right_med4_k&k.0
                        MOS.&distribution._right_med6_k&k.0
                        MOS.&distribution._right_med8_k&k.0;
        run;
        Proc transpose data = &distribution._K&K out = &distribution._K&K(drop=_NAME_);
                by MED P5MR;
                ID N;
                var Power;
        run;
        title "&distribution K=0.&K.0";
        Proc print data = &distribution._K&K noobs label; format _: 6.3; run;
%mend;



%SGPLOT(distribution=Weibull, K=6);
%SGPLOT(distribution=Weibull, K=7);
%SGPLOT(distribution=Weibull, K=8);

%SGPLOT(distribution=Lognormal, K=6);
%SGPLOT(distribution=Lognormal, K=7);
%SGPLOT(distribution=Lognormal, K=8);

%SGPLOT(distribution=Normal, K=6);
%SGPLOT(distribution=Normal, K=7);
%SGPLOT(distribution=Normal, K=8);

%SGPLOT(distribution=Uniform, K=6);
%SGPLOT(distribution=Uniform, K=7);
%SGPLOT(distribution=Uniform, K=8);



ods rtf file = "&folder\&dist Median=&MED K=&K..rtf" bodytitle;
%print(distribution=Weibull, K=6);
%print(distribution=Weibull, K=7);
%print(distribution=Weibull, K=8);

%print(distribution=Lognormal, K=6);
%print(distribution=Lognormal, K=7);
%print(distribution=Lognormal, K=8);

%print(distribution=Normal, K=6);
%print(distribution=Normal, K=7);
%print(distribution=Normal, K=8);

%print(distribution=Uniform, K=6);
%print(distribution=Uniform, K=7);
%print(distribution=Uniform, K=8);
ods rtf close;
```

APPENDIX D

Table D-1. Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.6 (Lognormal distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.045	0.223	0.126	0.344	0.239	0.257	0.355	0.362	0.440	0.467	0.353
	0.4	0.236	0.580	0.476	0.776	0.666	0.678	0.815	0.812	0.900	0.903	0.869
	0.5	0.449	0.820	0.770	0.937	0.902	0.899	0.958	0.962	0.982	0.985	0.984
	0.6	0.768	0.969	0.955	0.979	0.988	0.980	0.980	0.991	0.963	0.981	0.988
	0.7	0.964	0.971	0.985	0.933	0.961	0.931	0.926	0.948	0.886	0.915	0.940
	0.8	0.894	0.867	0.914	0.801	0.851	0.761	0.797	0.839	0.743	0.792	0.827
4	0.2	0.048	0.169	0.103	0.259	0.188	0.162	0.295	0.254	0.381	0.343	0.279
	0.4	0.176	0.472	0.411	0.682	0.595	0.578	0.749	0.735	0.851	0.844	0.796
	0.5	0.367	0.729	0.662	0.895	0.834	0.828	0.924	0.927	0.973	0.972	0.960
	0.6	0.638	0.932	0.896	0.984	0.977	0.972	0.989	0.992	0.998	0.999	0.997
	0.7	0.919	0.996	0.991	0.999	0.999	0.998	0.997	0.999	0.995	0.998	0.999
	0.8	0.994	0.992	0.997	0.976	0.990	0.981	0.971	0.984	0.949	0.971	0.979
6	0.2	0.175	0.207	0.202	0.283	0.240	0.199	0.343	0.266	0.417	0.355	0.304
	0.4	0.180	0.474	0.400	0.677	0.600	0.561	0.751	0.706	0.845	0.827	0.794
	0.5	0.360	0.703	0.665	0.876	0.826	0.804	0.930	0.916	0.971	0.963	0.956
	0.6	0.635	0.917	0.900	0.982	0.976	0.964	0.992	0.993	0.999	0.998	0.999
	0.7	0.922	0.994	0.993	1.000	0.999	0.999	1.000	1.000	0.999	1.000	1.000
	0.8	0.999	0.999	1.000	0.998	0.999	0.998	0.996	0.999	0.993	0.998	0.999
8	0.2	0.408	0.389	0.438	0.449	0.470	0.371	0.535	0.418	0.594	0.501	0.487
	0.4	0.378	0.567	0.551	0.739	0.697	0.635	0.813	0.766	0.886	0.864	0.842
	0.5	0.469	0.742	0.731	0.898	0.868	0.831	0.942	0.924	0.979	0.967	0.963
	0.6	0.680	0.923	0.919	0.987	0.983	0.966	0.994	0.992	0.998	0.999	0.998
	0.7	0.929	0.994	0.994	1.000	1.000	0.999	1.000	1.000	1.000	1.000	1.000
	0.8	0.999	1.000	1.000	1.000	1.000	0.999	1.000	1.000	0.999	1.000	1.000

Table D-2: Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.7 (Lognormal distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.008	0.048	0.034	0.110	0.070	0.063	0.117	0.106	0.172	0.159	0.106
	0.4	0.072	0.285	0.197	0.465	0.355	0.390	0.489	0.530	0.608	0.619	0.519
	0.5	0.197	0.529	0.419	0.697	0.591	0.641	0.699	0.750	0.783	0.811	0.720
	0.6	0.440	0.749	0.648	0.856	0.775	0.816	0.844	0.893	0.877	0.907	0.874
	0.7	0.677	0.878	0.831	0.896	0.895	0.870	0.886	0.933	0.855	0.909	0.926
	0.8	0.800	0.866	0.905	0.796	0.849	0.744	0.795	0.843	0.737	0.786	0.837
4	0.2	0.024	0.056	0.037	0.110	0.064	0.058	0.107	0.093	0.160	0.139	0.090
	0.4	0.057	0.227	0.173	0.411	0.312	0.297	0.462	0.423	0.593	0.541	0.469
	0.5	0.157	0.430	0.368	0.627	0.561	0.521	0.714	0.669	0.819	0.765	0.745
	0.6	0.353	0.666	0.643	0.838	0.827	0.769	0.909	0.890	0.958	0.928	0.935
	0.7	0.692	0.894	0.906	0.966	0.970	0.945	0.988	0.983	0.992	0.993	0.996
	0.8	0.954	0.986	0.993	0.977	0.991	0.979	0.970	0.985	0.945	0.965	0.982
6	0.2	0.161	0.128	0.142	0.153	0.149	0.099	0.165	0.118	0.200	0.163	0.121
	0.4	0.068	0.210	0.157	0.368	0.279	0.258	0.402	0.361	0.542	0.487	0.403
	0.5	0.127	0.379	0.300	0.591	0.487	0.466	0.646	0.614	0.775	0.727	0.669
	0.6	0.284	0.623	0.559	0.809	0.773	0.735	0.880	0.867	0.941	0.912	0.914
	0.7	0.608	0.879	0.873	0.964	0.959	0.944	0.988	0.981	0.997	0.995	0.997
	0.8	0.941	0.993	0.996	0.996	0.999	0.998	0.998	0.999	0.995	0.997	0.999
8	0.2	0.394	0.311	0.381	0.331	0.382	0.274	0.390	0.296	0.407	0.320	0.333
	0.4	0.273	0.317	0.326	0.461	0.415	0.331	0.525	0.432	0.628	0.540	0.500
	0.5	0.260	0.439	0.406	0.621	0.577	0.504	0.712	0.650	0.824	0.771	0.731
	0.6	0.362	0.663	0.617	0.844	0.822	0.775	0.904	0.891	0.959	0.941	0.933
	0.7	0.653	0.905	0.898	0.979	0.975	0.972	0.993	0.992	0.999	0.999	0.998
	0.8	0.959	0.999	0.998	0.999	1.000	1.000	1.000	1.000	0.999	1.000	1.000

Table D-3 Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.8 (Lognormal distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.005	0.022	0.020	0.043	0.031	0.019	0.050	0.032	0.074	0.044	0.033
	0.4	0.021	0.067	0.062	0.144	0.117	0.087	0.178	0.134	0.252	0.193	0.164
	0.5	0.043	0.142	0.125	0.253	0.212	0.157	0.288	0.246	0.378	0.334	0.283
	0.6	0.094	0.253	0.219	0.414	0.364	0.301	0.487	0.448	0.571	0.549	0.510
	0.7	0.210	0.491	0.465	0.661	0.649	0.571	0.734	0.750	0.771	0.797	0.809
	0.8	0.534	0.794	0.824	0.780	0.833	0.723	0.792	0.839	0.736	0.785	0.836
4	0.2	0.019	0.022	0.014	0.042	0.025	0.021	0.029	0.028	0.048	0.046	0.019
	0.4	0.014	0.073	0.044	0.146	0.101	0.075	0.155	0.119	0.228	0.173	0.140
	0.5	0.036	0.129	0.109	0.237	0.207	0.151	0.311	0.226	0.412	0.300	0.303
	0.6	0.095	0.253	0.256	0.399	0.404	0.297	0.540	0.409	0.654	0.513	0.532
	0.7	0.258	0.462	0.496	0.649	0.666	0.558	0.782	0.688	0.861	0.770	0.801
	0.8	0.623	0.779	0.834	0.880	0.914	0.845	0.926	0.914	0.923	0.916	0.951
6	0.2	0.157	0.098	0.119	0.088	0.108	0.061	0.095	0.054	0.096	0.066	0.061
	0.4	0.028	0.068	0.046	0.138	0.092	0.073	0.144	0.125	0.203	0.184	0.121
	0.5	0.033	0.141	0.094	0.266	0.187	0.176	0.292	0.257	0.408	0.355	0.285
	0.6	0.078	0.292	0.228	0.469	0.397	0.358	0.541	0.482	0.680	0.606	0.560
	0.7	0.253	0.552	0.513	0.737	0.721	0.655	0.839	0.799	0.917	0.862	0.877
	0.8	0.680	0.882	0.904	0.962	0.971	0.946	0.989	0.982	0.992	0.992	0.996
8	0.2	0.392	0.279	0.366	0.270	0.348	0.244	0.332	0.245	0.315	0.234	0.289
	0.4	0.240	0.194	0.230	0.235	0.245	0.169	0.267	0.193	0.305	0.237	0.214
	0.5	0.173	0.203	0.193	0.301	0.266	0.195	0.337	0.275	0.435	0.368	0.306
	0.6	0.145	0.301	0.251	0.495	0.414	0.369	0.538	0.516	0.680	0.639	0.558
	0.7	0.250	0.588	0.502	0.773	0.714	0.707	0.837	0.841	0.916	0.888	0.876
	0.8	0.660	0.910	0.901	0.978	0.973	0.971	0.993	0.990	0.998	0.998	0.997

Table D-4: Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.6 (Normal distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.139	0.454	0.358	0.655	0.556	0.540	0.722	0.701	0.824	0.820	0.770
	0.4	0.326	0.711	0.653	0.877	0.825	0.818	0.916	0.912	0.960	0.962	0.952
	0.5	0.506	0.858	0.833	0.946	0.934	0.922	0.966	0.974	0.967	0.981	0.985
	0.6	0.730	0.951	0.949	0.963	0.978	0.962	0.958	0.979	0.934	0.957	0.969
	0.7	0.925	0.957	0.976	0.908	0.940	0.901	0.900	0.923	0.842	0.882	0.915
	0.8	0.875	0.846	0.899	0.768	0.821	0.723	0.760	0.812	0.695	0.753	0.791
4	0.2	0.098	0.360	0.291	0.569	0.476	0.448	0.646	0.618	0.775	0.757	0.692
	0.4	0.253	0.635	0.562	0.838	0.764	0.749	0.880	0.874	0.950	0.949	0.926
	0.5	0.415	0.800	0.747	0.938	0.901	0.899	0.965	0.960	0.989	0.990	0.982
	0.6	0.638	0.936	0.913	0.991	0.983	0.975	0.992	0.994	0.996	0.998	0.999
	0.7	0.888	0.993	0.987	0.996	0.998	0.995	0.994	0.998	0.988	0.996	0.997
	0.8	0.991	0.988	0.995	0.967	0.983	0.973	0.959	0.980	0.934	0.958	0.970
6	0.2	0.088	0.344	0.272	0.552	0.461	0.426	0.648	0.594	0.777	0.743	0.693
	0.4	0.246	0.607	0.558	0.820	0.761	0.719	0.889	0.864	0.956	0.936	0.932
	0.5	0.408	0.780	0.745	0.930	0.905	0.876	0.966	0.955	0.990	0.986	0.984
	0.6	0.638	0.927	0.918	0.987	0.982	0.973	0.996	0.995	1.000	0.998	1.000
	0.7	0.893	0.993	0.992	1.000	0.999	0.998	1.000	1.000	0.999	1.000	1.000
	0.8	0.997	0.999	0.999	0.996	0.998	0.997	0.994	0.998	0.988	0.996	0.997
8	0.2	0.231	0.395	0.362	0.574	0.504	0.459	0.667	0.605	0.780	0.756	0.705
	0.4	0.303	0.618	0.578	0.821	0.765	0.723	0.891	0.860	0.959	0.941	0.934
	0.5	0.422	0.785	0.759	0.933	0.910	0.879	0.967	0.956	0.991	0.986	0.987
	0.6	0.646	0.927	0.920	0.989	0.984	0.972	0.997	0.994	1.000	0.999	0.999
	0.7	0.896	0.992	0.991	1.000	1.000	0.998	1.000	1.000	1.000	1.000	1.000
	0.8	0.997	1.000	1.000	1.000	1.000	0.999	0.999	1.000	0.998	0.999	1.000

Table D-5: Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.7 (Normal distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.044	0.216	0.143	0.390	0.287	0.293	0.429	0.441	0.566	0.559	0.450
	0.4	0.136	0.465	0.347	0.662	0.549	0.592	0.684	0.727	0.790	0.813	0.728
	0.5	0.262	0.627	0.521	0.803	0.710	0.744	0.801	0.857	0.857	0.892	0.840
	0.6	0.460	0.796	0.712	0.891	0.836	0.854	0.877	0.925	0.883	0.920	0.916
	0.7	0.690	0.885	0.860	0.882	0.895	0.855	0.867	0.915	0.822	0.879	0.908
	0.8	0.795	0.843	0.886	0.761	0.819	0.706	0.759	0.811	0.689	0.743	0.801
4	0.2	0.033	0.175	0.130	0.340	0.257	0.216	0.405	0.346	0.535	0.469	0.413
	0.4	0.111	0.369	0.317	0.581	0.516	0.466	0.683	0.622	0.811	0.746	0.709
	0.5	0.214	0.526	0.475	0.742	0.704	0.643	0.833	0.797	0.915	0.871	0.870
	0.6	0.391	0.718	0.697	0.882	0.881	0.821	0.944	0.925	0.976	0.957	0.964
	0.7	0.683	0.905	0.915	0.971	0.979	0.957	0.990	0.988	0.990	0.993	0.996
	0.8	0.940	0.983	0.993	0.966	0.984	0.968	0.961	0.978	0.926	0.957	0.973
6	0.2	0.028	0.153	0.105	0.300	0.215	0.191	0.345	0.301	0.483	0.426	0.347
	0.4	0.085	0.328	0.259	0.550	0.455	0.416	0.619	0.580	0.754	0.708	0.646
	0.5	0.174	0.486	0.416	0.710	0.648	0.600	0.794	0.764	0.886	0.851	0.827
	0.6	0.334	0.681	0.635	0.863	0.837	0.798	0.927	0.914	0.970	0.951	0.952
	0.7	0.607	0.892	0.885	0.971	0.969	0.958	0.991	0.989	0.997	0.996	0.998
	0.8	0.925	0.991	0.995	0.994	0.999	0.996	0.997	0.998	0.992	0.996	0.998
8	0.2	0.185	0.222	0.214	0.351	0.296	0.231	0.416	0.335	0.522	0.448	0.390
	0.4	0.162	0.350	0.308	0.560	0.492	0.428	0.653	0.603	0.784	0.730	0.680
	0.5	0.205	0.494	0.439	0.726	0.678	0.621	0.809	0.785	0.909	0.875	0.851
	0.6	0.358	0.713	0.662	0.890	0.870	0.835	0.945	0.932	0.981	0.971	0.970
	0.7	0.642	0.916	0.902	0.985	0.980	0.980	0.996	0.996	0.999	0.999	0.998
	0.8	0.943	0.998	0.998	0.999	1.000	0.999	1.000	1.000	0.998	0.999	1.000

Table D-6: Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.8 (Normal distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.013	0.069	0.049	0.142	0.109	0.081	0.176	0.136	0.250	0.193	0.154
	0.4	0.032	0.142	0.120	0.259	0.214	0.167	0.311	0.259	0.401	0.352	0.305
	0.5	0.067	0.210	0.183	0.355	0.314	0.245	0.426	0.382	0.504	0.469	0.433
	0.6	0.116	0.328	0.291	0.502	0.464	0.387	0.578	0.559	0.661	0.650	0.628
	0.7	0.239	0.537	0.508	0.683	0.685	0.601	0.741	0.776	0.760	0.799	0.824
	0.8	0.512	0.768	0.801	0.745	0.802	0.685	0.756	0.807	0.689	0.741	0.800
4	0.2	0.008	0.051	0.035	0.112	0.084	0.055	0.140	0.098	0.208	0.138	0.123
	0.4	0.029	0.114	0.093	0.224	0.192	0.133	0.304	0.214	0.420	0.293	0.295
	0.5	0.055	0.182	0.169	0.320	0.305	0.221	0.451	0.323	0.572	0.432	0.443
	0.6	0.118	0.289	0.310	0.479	0.484	0.363	0.633	0.503	0.750	0.620	0.632
	0.7	0.271	0.512	0.528	0.695	0.720	0.616	0.827	0.744	0.892	0.824	0.853
	0.8	0.618	0.800	0.844	0.892	0.923	0.854	0.927	0.925	0.911	0.920	0.952
6	0.2	0.005	0.051	0.031	0.115	0.070	0.054	0.129	0.104	0.196	0.155	0.105
	0.4	0.022	0.120	0.088	0.247	0.179	0.159	0.297	0.247	0.410	0.347	0.287
	0.5	0.044	0.206	0.163	0.377	0.297	0.265	0.453	0.389	0.584	0.509	0.457
	0.6	0.111	0.357	0.307	0.558	0.502	0.444	0.664	0.600	0.799	0.721	0.691
	0.7	0.285	0.605	0.573	0.796	0.786	0.716	0.885	0.861	0.949	0.907	0.921
	0.8	0.680	0.898	0.913	0.968	0.977	0.955	0.990	0.986	0.990	0.993	0.996
8	0.2	0.164	0.131	0.143	0.164	0.163	0.101	0.190	0.135	0.245	0.177	0.146
	0.4	0.097	0.152	0.128	0.260	0.204	0.158	0.298	0.248	0.411	0.353	0.283
	0.5	0.082	0.213	0.171	0.389	0.303	0.265	0.440	0.401	0.589	0.536	0.445
	0.6	0.119	0.362	0.290	0.591	0.496	0.465	0.660	0.635	0.789	0.759	0.695
	0.7	0.273	0.638	0.564	0.827	0.773	0.760	0.887	0.891	0.945	0.933	0.918
	0.8	0.658	0.923	0.909	0.983	0.976	0.978	0.995	0.995	0.998	0.998	0.998

Table D-7: Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.6 (Uniform distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.059	0.266	0.177	0.434	0.319	0.331	0.471	0.450	0.576	0.586	0.491
	0.4	0.242	0.561	0.468	0.727	0.657	0.664	0.792	0.772	0.876	0.870	0.824
	0.5	0.429	0.788	0.736	0.923	0.880	0.889	0.955	0.949	0.981	0.982	0.974
	0.6	0.987	0.995	0.994	0.995	0.995	0.993	0.990	0.998	0.981	0.990	0.996
	0.7	0.996	0.990	0.994	0.970	0.981	0.968	0.960	0.977	0.931	0.961	0.975
	0.8	0.900	0.904	0.934	0.851	0.886	0.793	0.849	0.875	0.813	0.851	0.883
4	0.2	0.038	0.183	0.126	0.336	0.253	0.226	0.385	0.340	0.499	0.467	0.397
	0.4	0.175	0.446	0.372	0.641	0.577	0.547	0.723	0.675	0.814	0.807	0.743
	0.5	0.357	0.681	0.627	0.851	0.796	0.802	0.906	0.883	0.947	0.948	0.917
	0.6	0.693	0.919	0.876	0.975	0.956	0.960	0.986	0.984	0.996	0.996	0.991
	0.7	1.000	1.000	1.000	1.000	1.000	0.999	0.999	1.000	0.999	0.999	1.000
	0.8	0.999	0.997	1.000	0.996	0.996	0.994	0.990	0.998	0.981	0.990	0.996
6	0.2	0.037	0.161	0.114	0.313	0.228	0.198	0.368	0.312	0.485	0.442	0.384
	0.4	0.159	0.437	0.359	0.626	0.559	0.541	0.722	0.660	0.819	0.784	0.740
	0.5	0.371	0.653	0.620	0.823	0.797	0.766	0.895	0.853	0.946	0.930	0.910
	0.6	0.674	0.899	0.879	0.971	0.960	0.951	0.987	0.985	0.996	0.996	0.992
	0.7	0.970	0.998	0.999	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.8	1.000	1.000	1.000	1.000	1.000	0.999	0.999	1.000	0.999	0.999	1.000
8	0.2	0.291	0.302	0.323	0.423	0.390	0.299	0.499	0.375	0.564	0.491	0.458
	0.4	0.314	0.493	0.463	0.665	0.625	0.561	0.747	0.668	0.834	0.796	0.751
	0.5	0.452	0.687	0.668	0.835	0.813	0.784	0.905	0.872	0.949	0.934	0.918
	0.6	0.744	0.903	0.902	0.968	0.965	0.952	0.991	0.983	0.995	0.995	0.992
	0.7	0.977	0.998	0.997	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table D-8: Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.7 (Uniform distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.016	0.079	0.052	0.168	0.117	0.098	0.184	0.186	0.277	0.267	0.197
	0.4	0.073	0.242	0.172	0.417	0.310	0.335	0.445	0.489	0.570	0.601	0.491
	0.5	0.180	0.470	0.371	0.645	0.540	0.584	0.662	0.711	0.725	0.780	0.683
	0.6	0.543	0.731	0.636	0.803	0.711	0.767	0.783	0.839	0.826	0.874	0.808
	0.7	0.624	0.847	0.757	0.890	0.853	0.855	0.885	0.914	0.896	0.931	0.918
	0.8	0.820	0.904	0.914	0.845	0.885	0.803	0.841	0.882	0.813	0.856	0.882
4	0.2	0.014	0.066	0.041	0.145	0.100	0.073	0.162	0.145	0.266	0.220	0.155
	0.4	0.055	0.203	0.148	0.351	0.285	0.251	0.425	0.379	0.557	0.494	0.432
	0.5	0.136	0.365	0.305	0.551	0.499	0.442	0.648	0.594	0.746	0.690	0.655
	0.6	0.354	0.600	0.572	0.750	0.761	0.670	0.854	0.807	0.908	0.872	0.874
	0.7	0.782	0.850	0.876	0.934	0.947	0.896	0.973	0.954	0.989	0.976	0.980
	0.8	1.000	0.999	1.000	0.994	0.995	0.995	0.992	0.995	0.984	0.991	0.996
6	0.2	0.016	0.055	0.035	0.129	0.079	0.062	0.141	0.120	0.224	0.190	0.125
	0.4	0.045	0.180	0.118	0.313	0.244	0.209	0.367	0.334	0.493	0.450	0.371
	0.5	0.116	0.330	0.252	0.496	0.421	0.384	0.572	0.525	0.672	0.638	0.581
	0.6	0.280	0.549	0.493	0.713	0.683	0.616	0.799	0.764	0.875	0.848	0.828
	0.7	0.665	0.839	0.846	0.931	0.933	0.896	0.970	0.956	0.992	0.979	0.982
	0.8	1.000	1.000	1.000	1.000	1.000	1.000	0.999	1.000	0.999	1.000	1.000
8	0.2	0.268	0.210	0.267	0.257	0.268	0.179	0.297	0.215	0.358	0.267	0.244
	0.4	0.203	0.248	0.240	0.367	0.331	0.245	0.434	0.367	0.542	0.467	0.400
	0.5	0.203	0.356	0.318	0.513	0.467	0.394	0.615	0.554	0.713	0.660	0.612
	0.6	0.338	0.576	0.550	0.741	0.722	0.661	0.838	0.806	0.902	0.877	0.854
	0.7	0.693	0.892	0.882	0.959	0.956	0.942	0.982	0.980	0.995	0.990	0.990
	0.8	0.996	0.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table D-9: Results of power analysis when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.8 (Uniform distribution)												
Median (hours)	**P5MR**	**Sample size**										
		_10	**_11**	**_12**	**_13**	**_14**	**_15**	**_16**	**_17**	**_18**	**_19**	**_20**
2	0.2	0.009	0.031	0.023	0.065	0.053	0.031	0.081	0.051	0.120	0.091	0.070
	0.4	0.027	0.070	0.057	0.144	0.113	0.084	0.178	0.128	0.253	0.190	0.162
	0.5	0.047	0.121	0.119	0.227	0.192	0.142	0.275	0.211	0.344	0.278	0.246
	0.6	0.131	0.205	0.200	0.313	0.283	0.221	0.375	0.322	0.476	0.409	0.373
	0.7	0.142	0.364	0.315	0.530	0.483	0.418	0.609	0.595	0.703	0.692	0.651
	0.8	0.641	0.864	0.871	0.837	0.879	0.795	0.841	0.880	0.813	0.856	0.882
4	0.2	0.003	0.017	0.009	0.048	0.024	0.019	0.050	0.038	0.081	0.063	0.033
	0.4	0.013	0.061	0.038	0.121	0.090	0.066	0.138	0.103	0.205	0.160	0.122
	0.5	0.031	0.112	0.080	0.195	0.159	0.114	0.249	0.185	0.342	0.251	0.231
	0.6	0.092	0.198	0.194	0.309	0.325	0.211	0.428	0.317	0.528	0.403	0.428
	0.7	0.303	0.374	0.415	0.523	0.564	0.428	0.673	0.562	0.755	0.654	0.675
	0.8	0.766	0.735	0.806	0.805	0.860	0.769	0.902	0.839	0.916	0.874	0.899
6	0.2	0.006	0.015	0.009	0.041	0.019	0.017	0.042	0.029	0.069	0.054	0.029
	0.4	0.010	0.049	0.028	0.110	0.069	0.050	0.120	0.101	0.189	0.160	0.106
	0.5	0.026	0.101	0.065	0.197	0.142	0.114	0.214	0.201	0.327	0.284	0.219
	0.6	0.074	0.238	0.164	0.368	0.298	0.271	0.421	0.382	0.541	0.480	0.426
	0.7	0.246	0.461	0.422	0.608	0.611	0.521	0.732	0.656	0.808	0.751	0.748
	0.8	0.773	0.824	0.860	0.913	0.939	0.880	0.966	0.940	0.986	0.970	0.978
8	0.2	0.261	0.178	0.247	0.181	0.220	0.141	0.215	0.139	0.214	0.146	0.159
	0.4	0.175	0.129	0.162	0.175	0.176	0.100	0.203	0.141	0.245	0.184	0.143
	0.5	0.134	0.144	0.135	0.214	0.185	0.128	0.253	0.206	0.338	0.282	0.223
	0.6	0.119	0.224	0.182	0.354	0.289	0.254	0.418	0.378	0.529	0.492	0.407
	0.7	0.223	0.485	0.419	0.652	0.594	0.564	0.730	0.701	0.803	0.794	0.748
	0.8	0.679	0.868	0.851	0.939	0.942	0.916	0.976	0.968	0.991	0.984	0.987

Figure D-1: Power curves of study design when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.6 (Lognormal distributions).

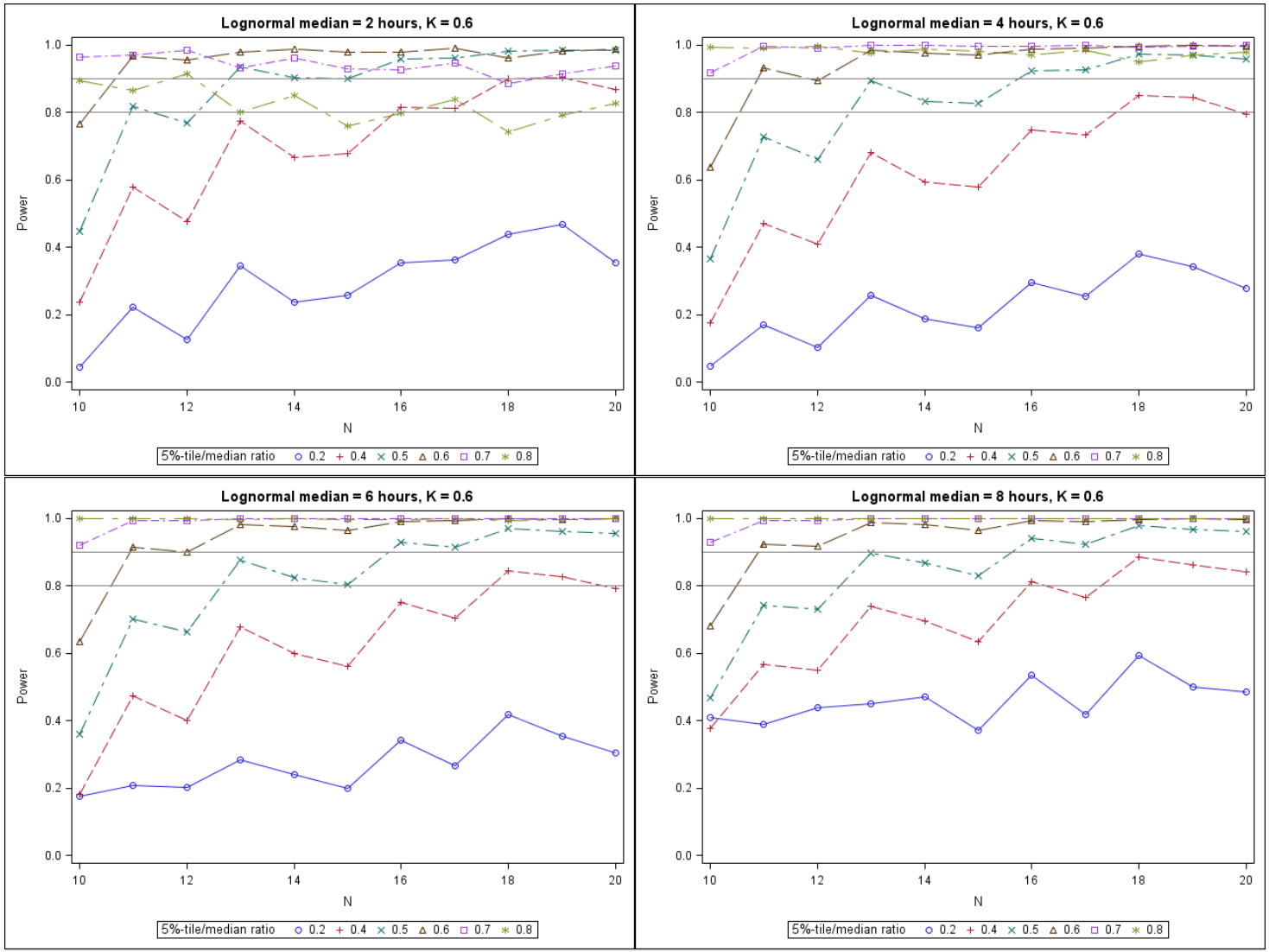


Figure D-2: Power curves of study design when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.7 (Lognormal distributions).

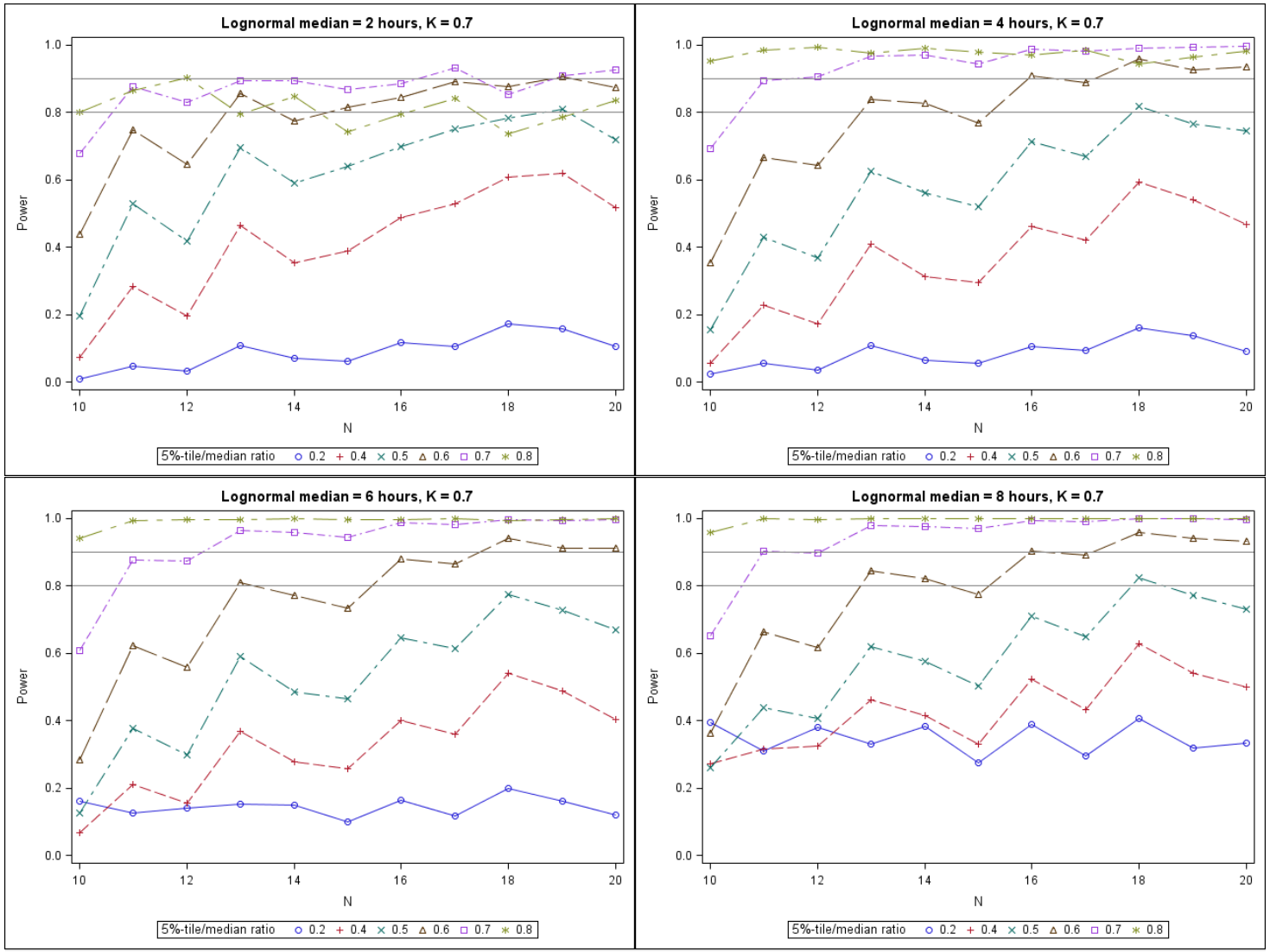


Figure D-3: Power curves of study design when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.8 (Lognormal distributions).

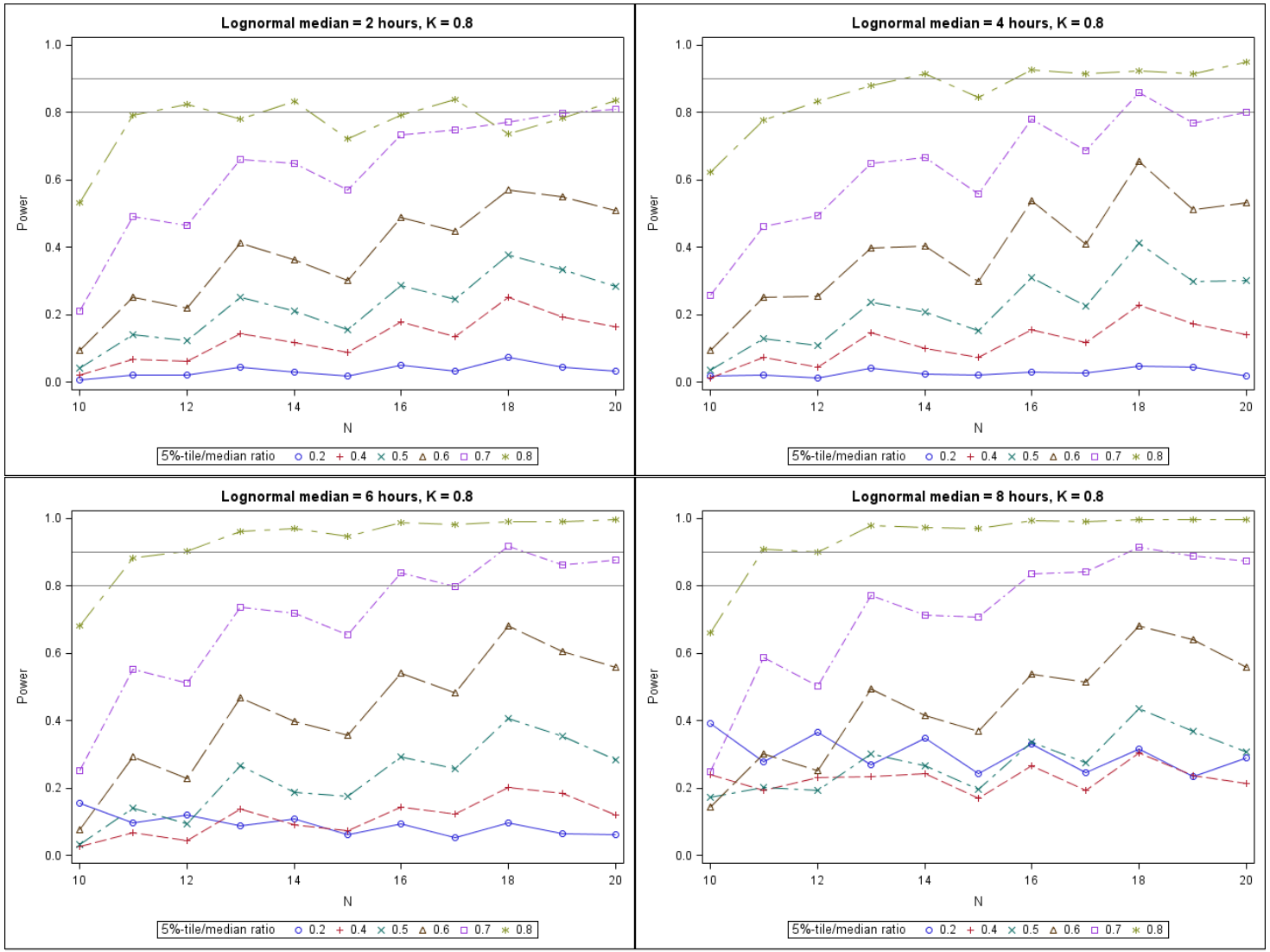


Figure D-4: Power curves of study design when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.6 (Normal distributions).

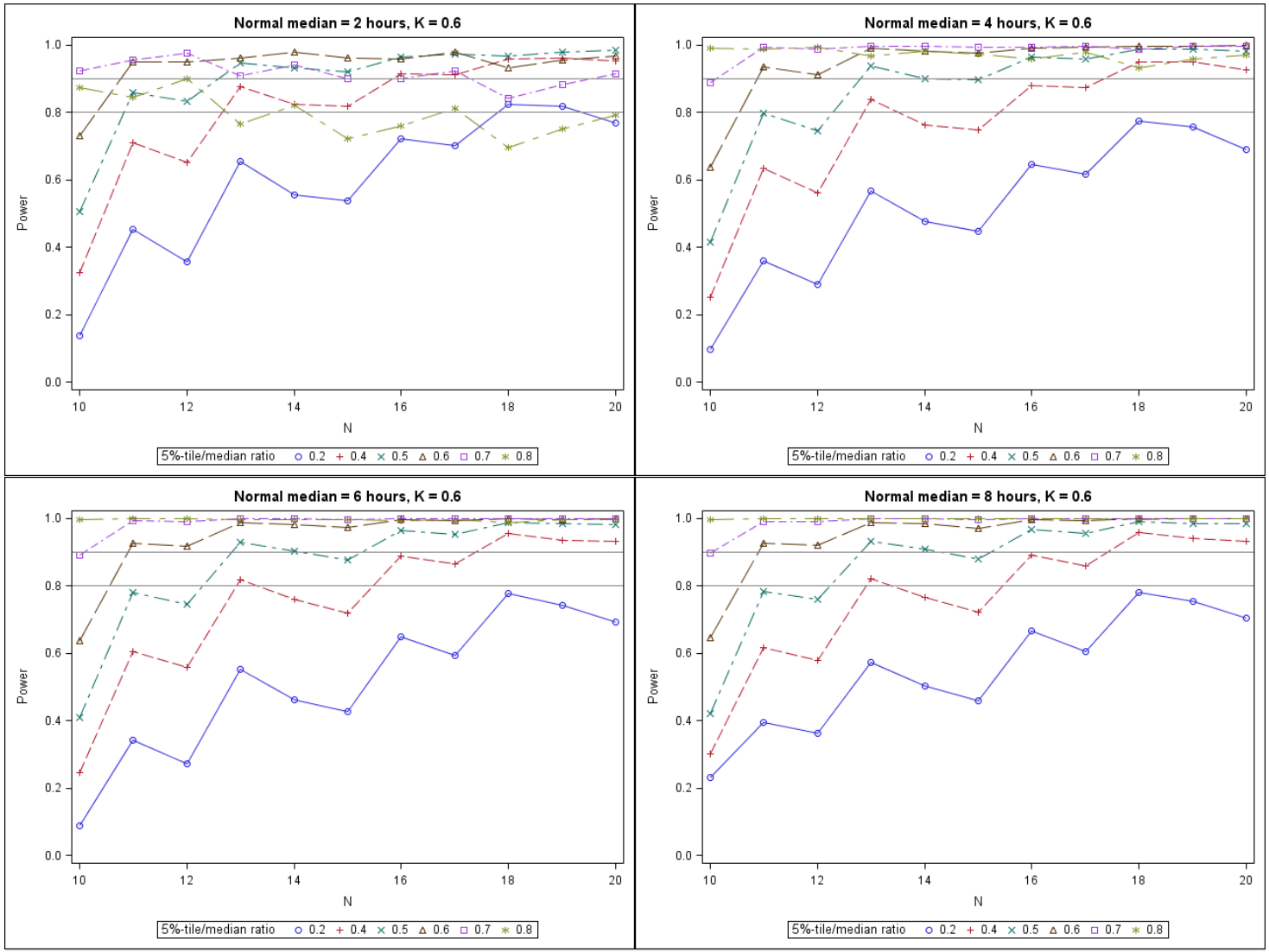


Figure D-5: Power curves of study design when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.7 (Normal distributions).

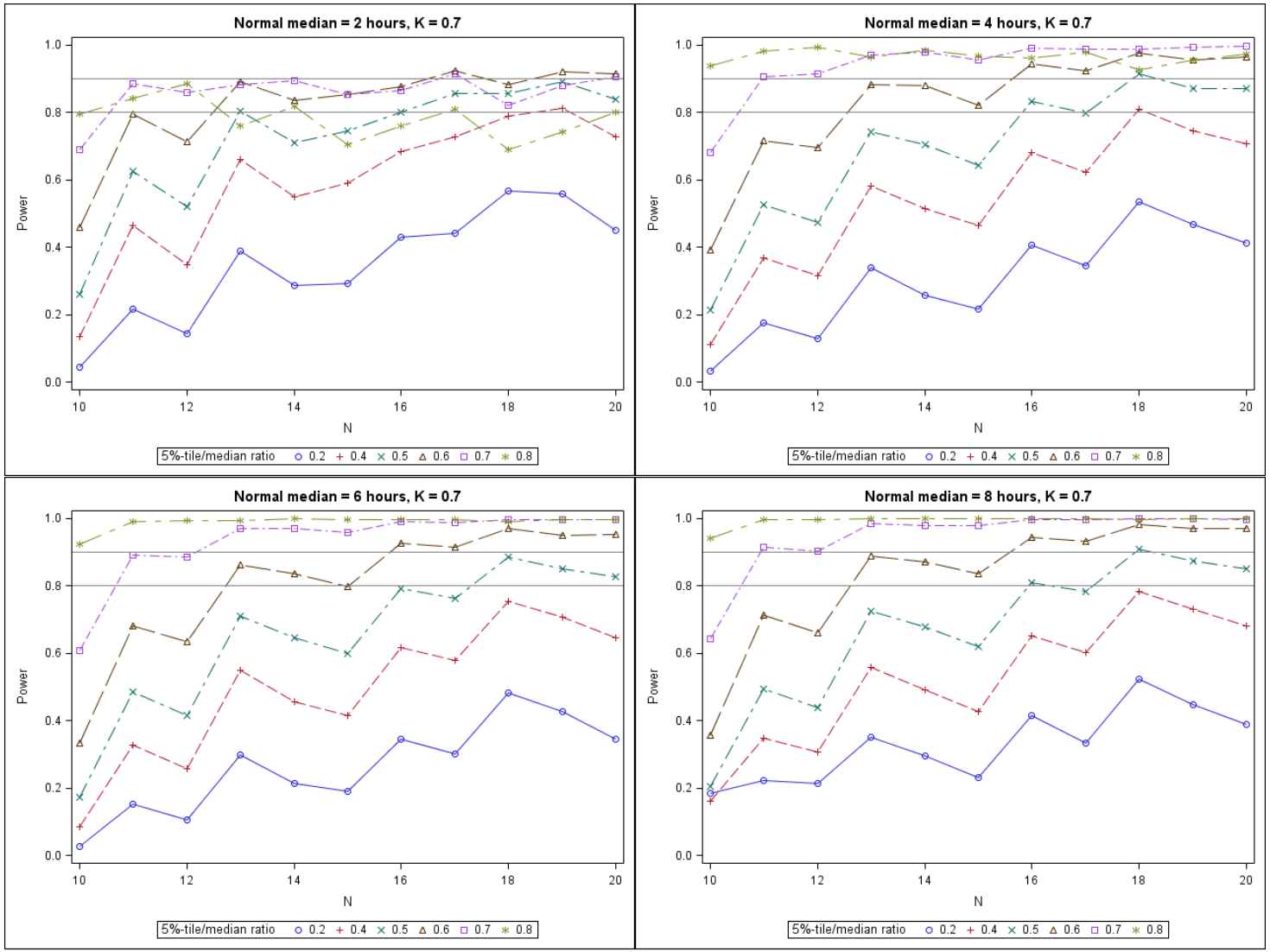


Figure D-6: Power curves of study design when the lowest acceptable ratio 95% LCL_{mCPT}/mCPT = 0.8 (Normal distributions).

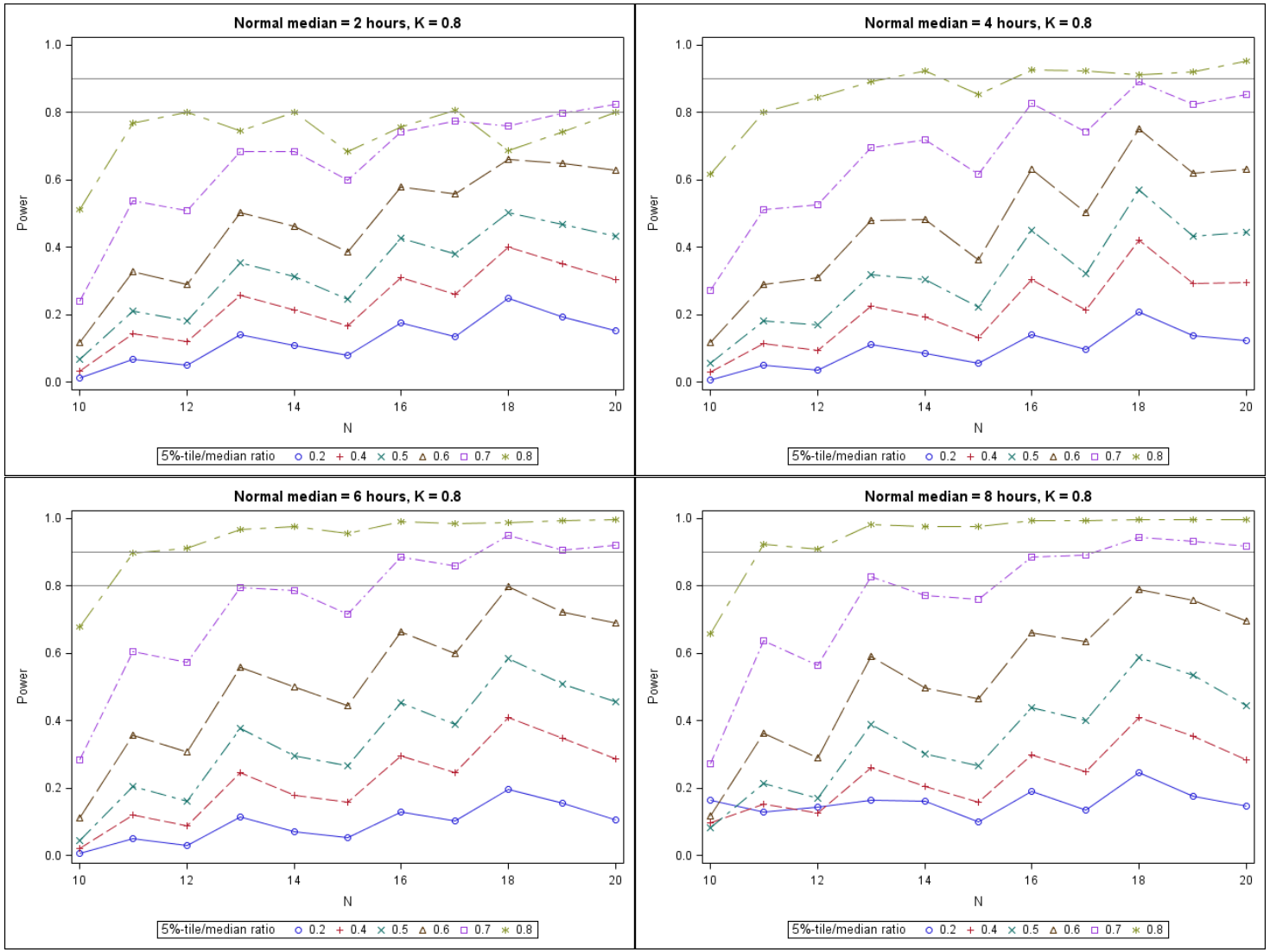
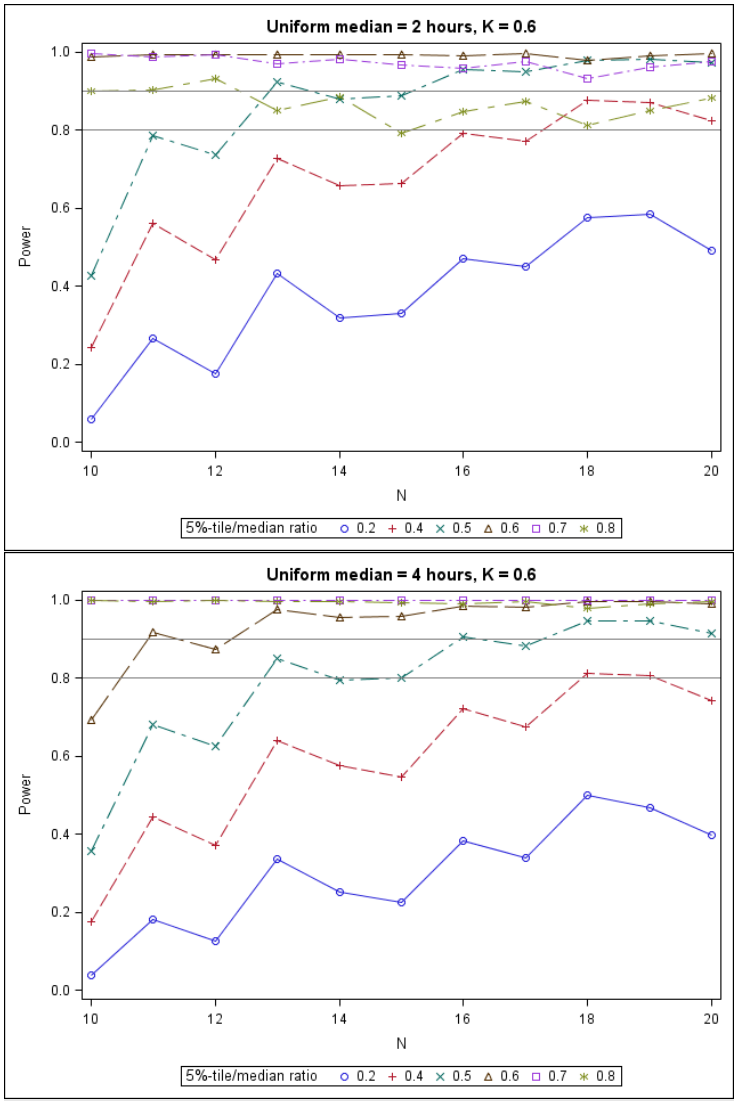
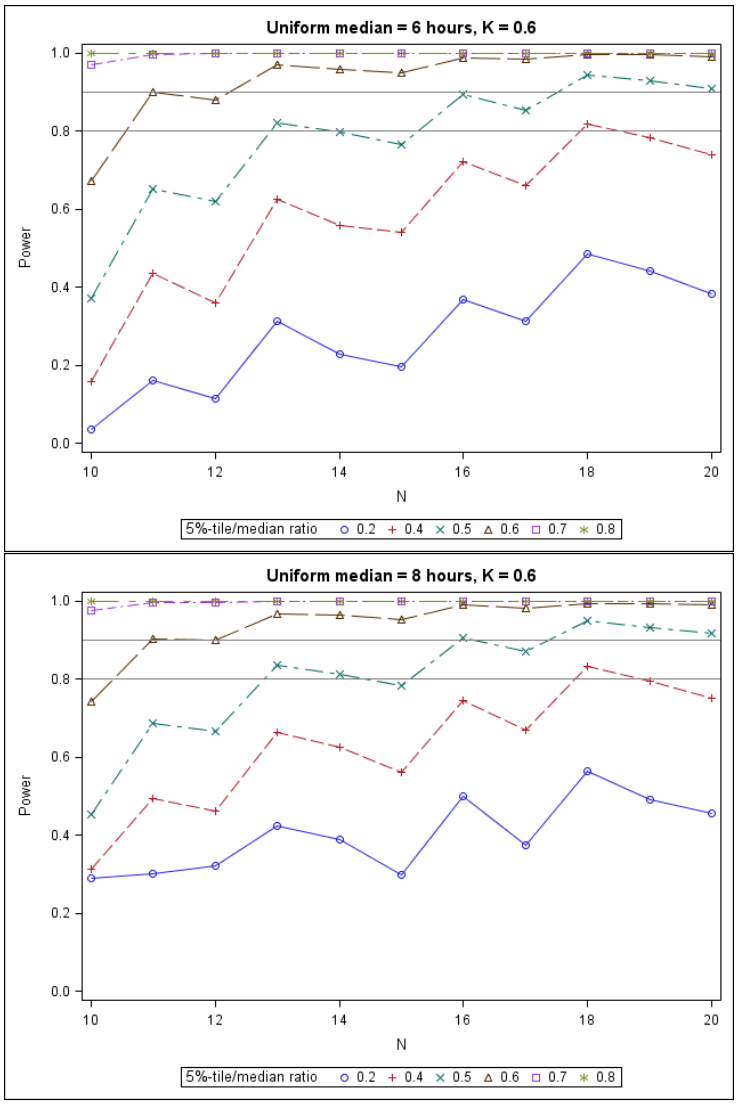


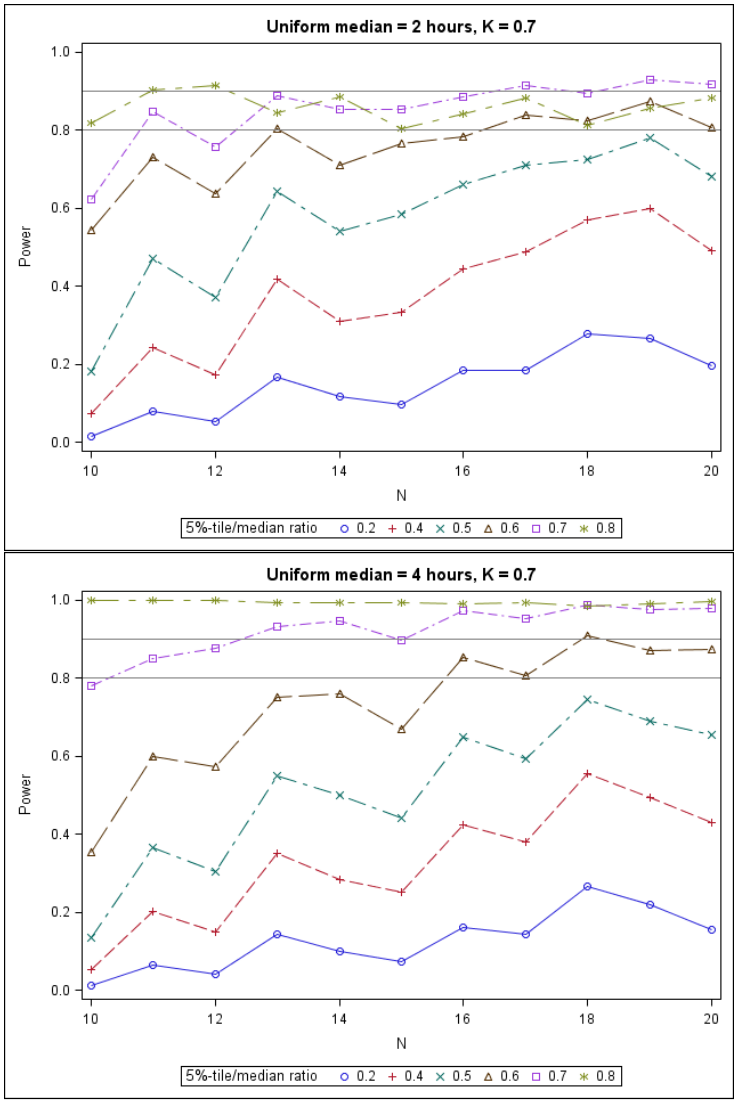
Figure D-7: Power curves of study design when the lowest acceptable ratio 95% $LCL_{mCPT}/mCPT = 0.6$ (Uniform distributions).

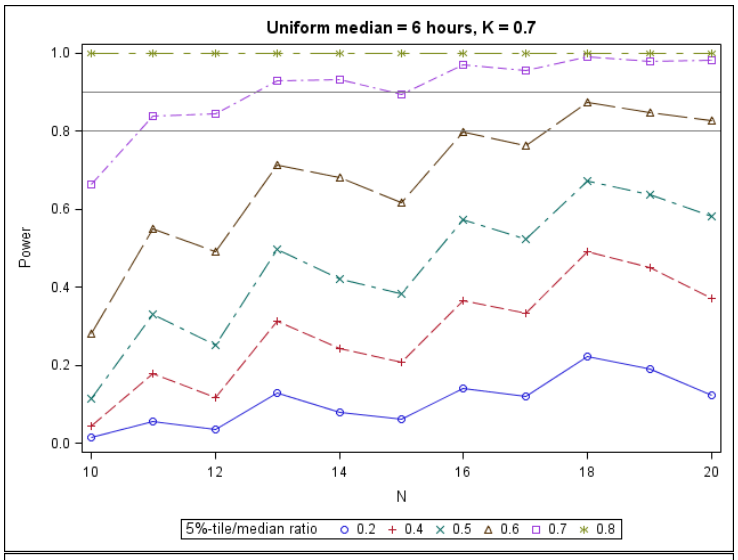



Uniform median = 6 hours, K = 0.6
Power
1.0
0.8
0.6
0.4
0.2
0.0
10
12
14
16
18
20
N
5%-tile/median ratio
0.2
0.4
0.5
0.6
0.7
0.8

Uniform median = 8 hours, K = 0.6
Power
1.0
0.8
0.6
0.4
0.2
0.0
10
12
14
16
18
20
N
5%-tile/median ratio
0.2
0.4
0.5
0.6
0.7
0.8

Figure D-8: Power curves of study design when the lowest acceptable ratio 95% $LCL_{mCPT}/mCPT = 0.7$ (Uniform distributions).




Uniform median = 6 hours, K = 0.7
Power
1.0
0.8
0.6
0.4
0.2
0.0
10
12
14
16
18
20
N
5%-tile/median ratio
0.2
0.4
0.5
0.6
0.7
0.8

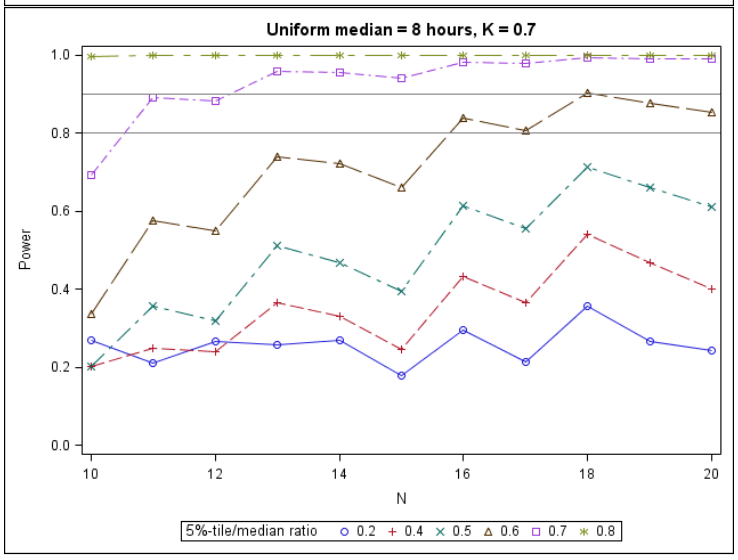
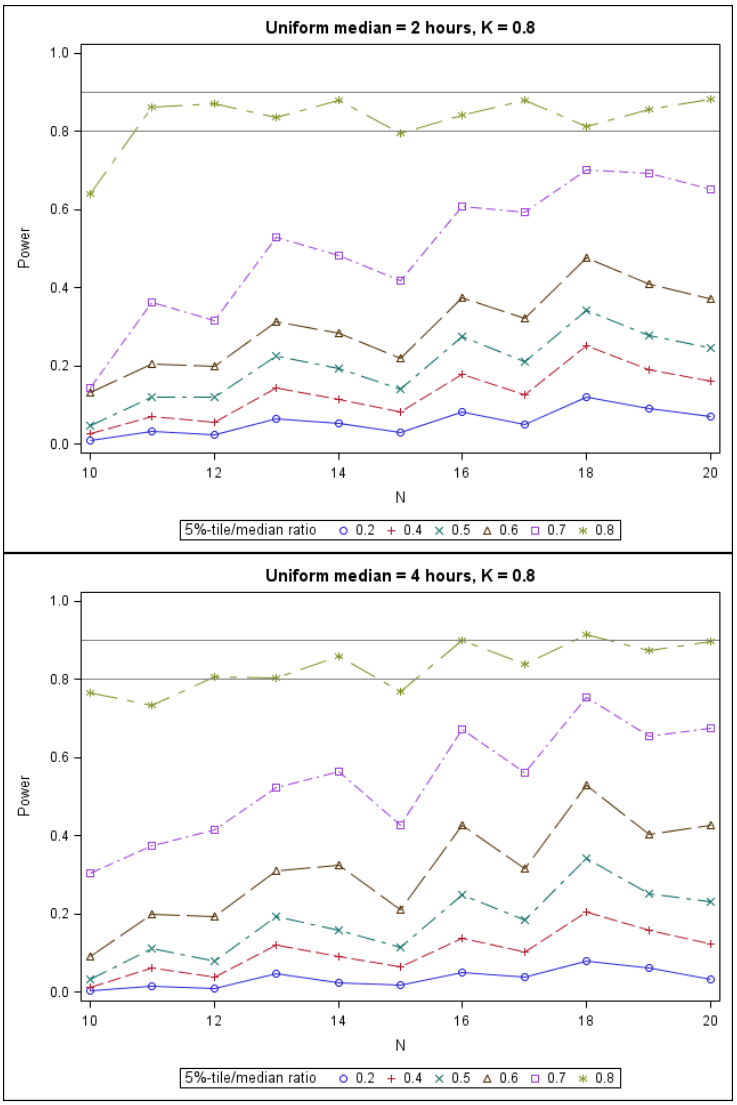
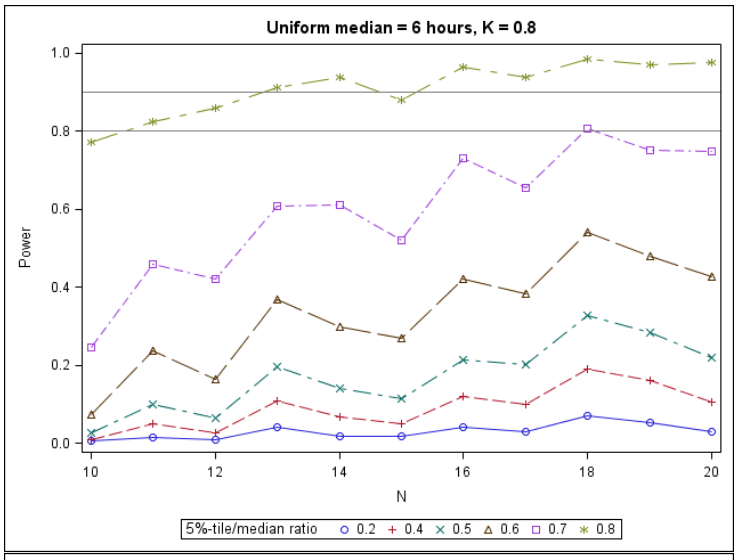
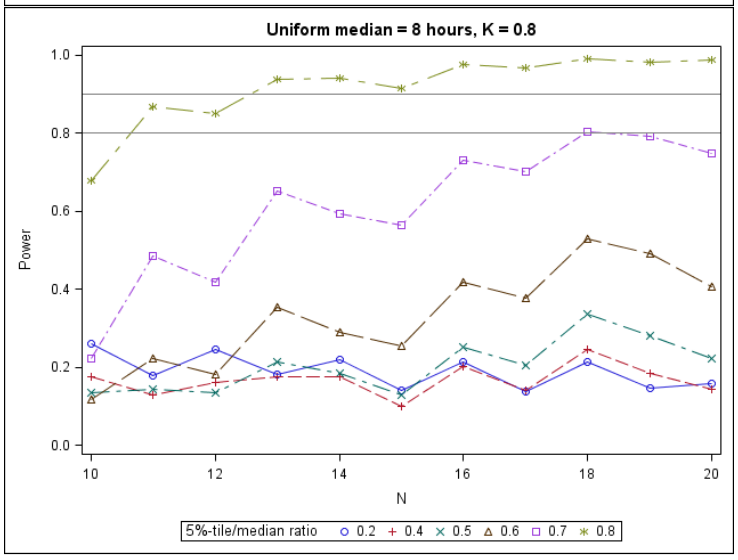

Uniform median = 8 hours, K = 0.7
Power
1.0
0.8
0.6
0.4
0.2
0.0
10
12
14
16
18
20
N
5%-tile/median ratio
0.2
0.4
0.5
0.6
0.7
0.8

Figure D-9: Power curves of study design when the lowest acceptable ratio 95% $LCL_{mCPT}/mCPT = 0.8$ (Uniform distributions).




Uniform median = 6 hours, K = 0.8
Power
1.0
0.8
0.6
0.4
0.2
0.0
10
12
14
16
18
20
N
5%-tile/median ratio 0.2 0.4 0.5 0.6 0.7 0.8


Uniform median = 8 hours, K = 0.8
Power
1.0
0.8
0.6
0.4
0.2
0.0
10
12
14
16
18
20
N
5%-tile/median ratio 0.2 0.4 0.5 0.6 0.7 0.8

ATTACHMENT 5
EPA Standard Rate of Application

Test products should be applied at 1 g/600 cm^2 for aerosols and wipes. For pump sprays the Agency recommends applying 0.5 g product/600 cm^2. These application rates are based on dosimetry tests used in previous studies since 2006, which have been reviewed by EPA and HSRB.

In April 2015, the HSRB reviewed a protocol conducted by SC Johnson and agreed to the use of the EPA's standard application rate to replace dosimetry testing.[14]

Table 1. Combined results of dosimetry testing from skin-applied repellent studies reviewed by EPA and HSRB since 2006 for three formulation types.

Formulation Type	**Total No. of Subjects in Dosimetry Phase for Mosquito Tests**	**Mean Dose (g/600 cm^2) $\pm$ 1 SD**	**Dose range (g/600 cm^2)**
Lotion	112	0.933 $\pm$ 0.299	0.63-1.23
Pump spray	92	0.434 $\pm$ 0.113	0.32-0.55
Aerosol	25	0.815 $\pm$ 0.262	0.55-1.08

[14] Dawson, Liza. April 22-23, 2015 EPA Human Studies Review Board Meeting Report. https://www.epa.gov/sites/production/files/2015-06/documents/hsrb_april_2015_meeting_final_report.pdf. p. 12.