Summary Outline of 40 CFR § 26.1125, Containing Information and Commentary Addressing the Requirements of Each Subsection.

§ 26.1125 Prior submission of proposed human research for EPA review

§ 26.1125(a): A discussion of:

§ 26.1125(a)(1): The potential risks to human subjects.

We consider two classes of risks to be pertinent:

1. Risks of exposure to insect repellent formulations; and
2. Risks from exposure to mosquitoes or mosquito-borne pathogens in a field setting.

§ 26.1125(a)(2): The measures proposed to minimize risks to human subjects.

1. Minimization of risks from exposure to insect repellent formulations.

The potential risks to humans exposed to the three formulations containing IR3535 are expected to be negligible based on a history of over 20 years of use of the active ingredient in a variety of insect repellent products in Europe (see EPA Fact Sheet, *Appendix 6*). Also, IR3535 is the active ingredient in several lotion, spray and aerosol formulations currently in use by consumers in the U.S. (see Technical Sheet, *Appendix 7*, and EPA Registration Nos. 806-13; 14; 16 to 28). The formulated products listed are all based on IR3535 Technical obtained from the proposed registrant for the current formulations intended for efficacy testing. The WHO assessment also provided in this package (*Appendix 8*) reviews the broad range of animal and human safety data that support the lack of significant adverse effects that characterize IR3535. Further information is provided in the Materials Safety Data Sheets ("MSDSs") and formulation information provided for each formula (*Appendix 9A – 9D*) are comparable to those for equivalent consumer products in common use. It is also important to note that all of the inert ingredients contained in the products are either listed on EPA Inerts Lists 4A or 4B or are common ingredients found in many cosmetic and other consumer applied products currently on the market. These types of inerts are considered to have a very low degree of toxicity and irritancy and would, thus, pose insignificant risks to test subjects. Exclusion criteria are exercised to minimize risk of including volunteers with allergies to common fragrances or cosmetic ingredients. Lastly, most tests are conducted only once, and as a result, most participants are exposed to a particular formulation, or particular active, only once or twice by our testing program on an annual or multiple-year basis.

2. Minimization of risks from exposure to mosquitoes or mosquito-borne pathogens in a field setting.

Because our volunteers are life sciences students, professional biologists, mosquito control workers and others actively engaged in outdoor pursuits, participation in our field studies does not increase their risk of mosquito exposure beyond that which they would normally experience (see recruitment procedure details, *Appendix 11*). Further, the Study Director excludes individuals known to have allergies to mosquito bites. We take many steps to minimize the probability that volunteers will experience mosquito bites. These steps (from Protocol C-L-001, which provides general test procedures, *Appendix 1C*) include the following:

a) A qualified supervisor is present during all phases of the efficacy test.
b) In field tests for registration, efficacy is normally demonstrated in prior laboratory tests by sponsors using caged mosquitoes. Accordingly, many participants typically receive no arthropod bite attempts, and few ever receive more than 5 bite attempts. No bite attempts occur during tick tests due to tick behavior (below).
c) Test participants are typically college-educated, vigorous individuals with field experience and training in the life sciences. A substantial portion of test participants has research experience and expertise in statistical thinking that aids in personal risk evaluation.
d) Participants are provided with and required to wear protective clothing and safety equipment.
e) Participants are instructed as to how to detect the initiation of biting by mosquitoes or other flies. Participants are directed to quickly remove arthropods before being bitten.
f) Participants work in pairs in field tests and are charged with monitoring for alighting arthropods on their partner throughout the test.
g) Participants in field tests are provided with hand-held electric entomological aspirators to quickly remove any mosquitoes that alight, before biting.
h) All test participants are orally informed of the risks of disease contraction in a clear and objective manner by the Study Director in advance of signing Consent Form, during pre-test meetings, immediately prior to the test, and during the conduct of the test. Mosquitoes: Mosquito-vectored pathogens such as Western Equine Encephalitis and West Nile Virus are rare all test sites. State and local (mosquito abatement district) vector-borne disease data are monitored in advance of test date in the event that a true risk is ever indicated. Tests will not be performed if there have occurred more than one conversion in the nearest sentinel chicken flocks within one month of a test date. For laboratory testing, we rear disease free arthropods or obtain them from commercial and academic sources that specialize in their production for biomedical research. Ticks: We conduct tick studies with unfed nymphal and adult ticks. At intervals of fifteen minutes, each participant places a tick on the hand with an artist's paintbrush. Ticks are observed as they approach the adjacent treated area of the arm, which begins at the wrist. Ticks are scored as crossing the repellent barrier if they move at least 2 cm into the treated area (toward the elbow) within three minutes. During this period, ticks are "questing" rather than feeding; feeding takes over an hour to

initiate after site attachment, such that ticks in our study present no risk of biting. Ticks are contained in snap cap vials before and after testing, following the protocol of CDC.

i) Untreated control individuals are always Study Directors or experienced management personnel.

j) Participants may withdraw from testing at any time for any reason without penalty, and they are informed of this fact in advance and during the test.

k) Individuals that display unanticipated dermal sensitivity to any bites inadvertently received during testing are removed from further exposure without penalty to their compensation for participation in that test.

l) At the discretion of the Study Director, any participant not adhering to test and safety guidelines during the test will be withdrawn from participation.

m) A complete first aid kit is maintained and carried by the Study Director. Participants are informed of its presence and location. Contact information for the nearest emergency medical facility (field: Rideout Hospital, 726 4th Street, Marysville, CA, telephone 530-749-4300; lab: (Sutter Davis Hospital, 2000 Sutter Place – Covell Blvd at Hwy 113, Davis 530-756-6440) is distributed to participants and posted at the study site during each test.

n) The Study Director carries a cellular telephone to contact emergency officials as needed.

o) Lastly, the risk of boredom and its associated problems such as distracting or detrimental behavior is lessened by the recruitment of groups of associated individuals who enjoy being together and who are aware of the importance of doing a good job (e.g., graduate students studying medical entomology).

§ 26.1125(a)(3): The nature and magnitude of all expected benefits of the proposed research, and to whom they would accrue.

The expected benefits of the proposed efficacy study will be to users of the insect repellent products. Determining the period of efficacy will allow for accurate labeling of the product to specify the time period of effective protection and the number of applications that will be needed to provide protection from biting insects and insects that can be vectors of serious human diseases.

Insect repellents permit people to be active in the presence of blood-feeding arthropods. They do so by reducing the risks of serious discomfort, systemic reactions to arthropods salivary proteins, and contraction of arthropod-borne diseases such as West Nile fever, Lyme disease, malaria, and dengue fever. Diseases transmitted by insects are a major source of mortality and morbidity worldwide, especially in tropical climates. Global climate change and newly emerging infectious diseases are likely to further increase the importance of such mortality and morbidity in temperate regions in the near future.

Exposure to risks associated with biting arthropods may be reduced by public health measures that decrease pest population size, decrease susceptibility to pathogenic

infection (e.g. vaccines), and by personal prevention measures. Personal prevention measures, including behavioral avoidance and use of repellents require little preparation, are generally inexpensive, and are the most flexible (Debboun et al. 2005). Yet lack of public awareness and public education has led to a recent decline in the use of repellents in the US relative to the risk from, e.g., West Nile virus and the Lyme borrelia (L. Lungren, CDC, pers. comm.).

In 2005 Centers for Disease Control staff founded the CDC Repellents Working Group to combat this problem. Upwards of 50% of the US population reports rarely or never using insect repellent. DEET-based repellents have been the industry-standard for several decades, yet rare, serious health-risks associated with their use, plus cosmetic discomfort, has eroded public confidence in the safety of DEET (Fradin and Day 2002). Additional information comes from military insect repellent development programs. Military data suggest that approximately 70% of infantry avoid applying DEET even when ordered (LTC M. Debboun, U. S. Army, personal communication). This despite the fact the more than half of all military medical admissions in the Iraq theater in 2003-2005 were from severe reactions to insect bites (LTC M. Debboun, U. S. Army, personal communication).

The US military invested $5,000,0000 from the year 2000-2005 to develop new DEET-alternatives. In 2005, it was determined that focus would instead shift to working with such products already developed, marketed and registered in the US, including IR3535 (Debboun 2005). IR3535 has an excellent safety profile (documents herein), broad consumer acceptance (e.g., the Avon Bug Guard line of repellents), and is more effective than DEET in repelling certain insects (including those responsible for the discomfort and disease in US troops in Iraq; Naucke et al. in press). Yet until now little effort has been made to refine IR3535 products in the manner which led to the ultimate high efficacy and original consumer acceptance of DEET (Carroll in press).

References for this section (attached as *Exhibits 12A – 12D*):

Carroll SP. In press. Evaluation of topical insect repellents and factors that affect their performance. In *Insect Repellents*, Debboun, M., Frances, S., and Strickman, D. (eds.). Boca Raton, CRC Press.

Debboun M, Strickman DA and Klun JA. 2005. Repellents in the military: our first line of defense. *Journal of the American Mosquito Control Association* 21:4-6.

Fradin MS, Day JF. 2002. Comparative efficacy of insect repellents against mosquito bites. *New England Journal of Medicine* 347:13-18.

Naucke TJ, Lornentz S, Grünwald H-W. In press. Laboratory testing of the insect repellents IR3535 and DEET against *Phlebotomus mascittii* and *P. duboscqi* (Diptera: Psychodidae). *International Journal of Medical Microbiology*.

§ 26.1125(a)(4): Alternative means of obtaining information comparable to what would be collected through the proposed research.

There are no accepted alternatives for obtaining efficacy information that we are aware of that would be acceptable for registration of these products. In April 2000 US EPA convened a Scientific Advisory Panel ("SAP") guide the Agency in the modernization of its scientific requirements for the collection of data to support the registration of new insect repellents (Insect Repellent Product Performance Testing Guideline, OPPTS 810.3700; and SAP Report No. 00-02B, August 2, 2000, Insect Repellents for Human Skin and Outdoor Premises, *Appendices 10A – 10B*). In their evaluation, the SAP concluded that field testing of insect repellents by human volunteers was critical and fundamental to the evaluation of their performance by the US EPA.

§ 26.1125(a)(5): Balance of risks and benefits of the proposed research.

The precaution taken to minimize the risks of biting mean that volunteers are probably no more, or less likely to receive mosquito bites that they would from participating in an ordinary summer hike, picnic or barbecue. The PI has conducted dozens of field efficacy trials since 1989, with no incidents of injury or disease. These facts, combined with the long history of safe use of IR3535 products in the U.S. and around the world, indicate that risks of the research are negligible compared to the substantial benefits in providing accurate application instructions to consumers to provide effective protection from insects that have significant health implications.

§ 26.1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.

This information consists solely of the revised Informed Consent Forms ("ICFs") for studies EMD-003 and EMD-004, attached as *Appendices 2A – 2B*.

These ICFs were based on those for similar, prior studies that were written by IIRB. No changes were required to the ICFs for EMD-003 or EMD-004 by IIRB, Inc. During the IRB review process for the present studies, minor changes to the ICFs were initiated by the Study Director in an email to Ms. Debbie Siano of IIRB on 18 April 2006. Those changes were either clerical corrections or efforts to improve clarity and comprehensiveness. That email (appended as correspondence in *Appendix 5*) read:

Debbie,
I have made the following corrections to the ICFs for EMD-003 and -004. Should you need me I will be reachable on my cell at 530-902-8267, and then back at my desk by 4 your time. Thanks!

EMD-003

Page 1

Title of Study:
-Corrected number

Sponsor:

Nature and Purpose:
-Corrected sponsor

Page 2
Study Design:
-Changed to three test materials.

EMD-004

Page 1

Sponsor:
-Corrected sponsor

Nature and Purpose:
-Changed to field test of mosquitoes
-Corrected sponsor

Study Duration: Changed to field site

Page 2
Study Design:
-Changed to three test materials.
-Included lower legs (this is a mosquito study thing).
-Removed reference to receiving no material on one limb because it implies that the some subjects will be exposed without protection without their control. Normally, I am the untreated control. On occasion one of my highly experienced (> 10 years) technicians joins me with full knowledge in that role as a second untreated control subject. Is there a way we can write in leeway to have that second, experienced subject? If we can't come up with a way to do that now I could forego having the possibility of a second untreated control for the time being.

Procedures: I added lower legs under the application procedure
-Also added: If any mosquitoes land you will remove them immediately. (How is that?). Could also say 'If any mosquitoes land you will remove them immediately with a hand-held suction device.'

Risks and Discomforts:

-Added: **Measures will be implemented to remove mosquitoes before they have an opportunity to bite.**

§ 26.1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.

The following information is compiled from Protocol C-L-001 (*Appendix 1C*) and IIRB Site Questionnaires EMD-003 and EMD-004 (*Appendix 11*).

Our volunteers are mainly University of California–Davis graduate and undergraduate students in life science programs with which the Principal Investigator is associated. As a group, college students possess the flexible schedules, physical vigor and enthusiasm for unusual experiences that makes them ideal candidates for efficacy studies. Upon study initiation, we contact individuals who participated in previous Carroll-Loye repellent efficacy tests by selecting them from a Volunteer Database, which is maintained and accessed solely by the Principal Investigator, with the permission of those listed. At that time interested individuals often ask if one or more of their lab mates or classmates can participate as well. Students in his laboratory who depend on the Study Director directly for employment or scholastically are not eligible to participate.

A second subgroup of participants consists of staff and faculty members of local educational institutions and other college-educated adults from northern California who are similarly interested in scientific research also participate. A third group consists of mosquito and vector control professionals.

§ 26.1125(d): A description of circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.

The following information is from IIRB Site Questionnaires EMD-003 and EMD-004, attached as *Appendix 11*, and from the Efficacy Test Protocols, attached as *Appendices 1A – 1C*.

All potential participants are screened or re-screened for suitability for each test in a private, one-on-one conversation held at the office of the Principal Investigator (PI). The Exclusion Criteria (section 9.1.2 in both EMD-003 and EMD-004, *Appendix 1A – 1B*) are exercised by asking each candidate to address them in the interview with the PI. It is explained that pregnancy will be assessed directly in on the test day. The PI encourages candidates to ask questions and ask for clarification at any time during the interview and in all activities that follow. To candidates that pass screening the PI describes the test purpose in plain language (in English), and the procedures and comportment to be followed are described in detail. Candidates are then asked if they would like to retire from consideration at that point. If they wish to remain in consideration, it is explained

and emphasized that they may withdraw from the test at any time during the test without penalty to their compensation. Candidates are given copies of the State of California Department of Pesticide Regulation 'Experimental Subjects' Bill of Rights' to read as the PI reads it aloud. They are also given a copy of the IRB-approved consent form to read as the PI reads it aloud. The amount and form of compensation is described. They are again encouraged to ask any questions they have about the test, which may include understanding its purpose more fully, understanding risks and discomforts more fully, and understanding treatment and compensation for injury more fully. While the majority of our subjects have worked with us on an occasional basis for a number of years, we encourage them to personally evaluate their interests and concerns about participation seriously each time. We ask them not to sign on immediately but to give the situation due consideration (normally at least one day, sometimes less for those who have participated in multiple prior studies). Because most of the volunteers are researchers and/or have advanced degrees in life sciences, we regard their motivations and decisions to participate as being unusually well considered and well informed. Accordingly, we normally accept their decisions to participate if they so choose following due consideration. Nonetheless, the PI retains the final right to refuse participation to any candidate.

§ 26.1125(e): Correspondence between the IRB and the Principal Investigator.

Cover letters from the IRB to the PI that accompanied approved ICFs are given in ICF files in *Appendices 4A – 4B.* Email correspondence associated with the review of EMD-003 and EMD-004 is given in *Appendix 5*.

§ 26.1125(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.

Cover letters from the IRB to the PI that accompanied approved Research Protocols and ICFs are included in *Appendix 4A – 4B.*