EU Workshop on Repellents
22nd – 23rd June 2015

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Director of ARCTEC
World-leading independent test centre for consultancy, evaluation and development of arthropod pest control technologies - testing of commercial products since the 1980's - more than 60 years of combined experience in insect control

Committed to quality
Services – consultancy, development and evaluation
- Laboratory repellent clinical trials
- Field repellency trials
- WHOPES Phase I, II, III
- Headlice products
- Afterbite products
- Animal products (e.g. equine)
- Behavioral olfactometry, trapping

Committed to quality science
Insectaries

- 12 different mosquito strains of the genera Aedes, Anopheles and Culex
- Bed bugs
- Cockroaches
- Triatomine bugs
- Sand flies
- House dust mites
- House flies
- Stable flies
- Clothes moths
- Ticks
- Head lice, Culicoides midges and other arthropods available on demand

Committed to quality science
The Team
Vector-borne diseases

- Vector-borne diseases account for 17% of all infectious diseases

- Malaria: endemic in 91 countries; half the world’s population at risk; 600,000 deaths

- Dengue: 2.5 billion people in over 100 countries are at risk

- Chikungunya: 2013 – shift to the Americas – 45 countries/territories; 1.7 million cases

- Filariasis, Jap Encephalitis, Chagas, leishmaniasis, sleeping sickness, etc, etc
Mosquitoes

*Anopheles* (malaria)
*Aedes* (dengue, chikungunya, yellow fever)
*Culex* (filariasis, West Nile virus)
The Zika virus

- Zika is a flavivirus transmitted by the *Aedes* genus of mosquitoes which also carry dengue, chikungunya and yellow fever.

- Some sexual transmission occurs.

- Symptoms of Zika are usually mild and may include a rash, itching, fever, muscle pain, conjunctivitis.

- Two conditions which are strongly suspected of being associated with Zika are especially worrying: microcephaly and Guillan-Barre syndrome.
- Only 20% of people will develop symptoms
- High risk group: pregnant women
- The risk is to the unborn child
- Transmitted via mosquito bite and sexual contact
- GB syndrome
The main vectors

*Aedes aegypti* (lyre)

*Aedes albopictus* (dorsal line)
Aedes aegypti

- Highly adapted to urban environment
- Aggressive biters – even through clothing
- Bite during day and night
- Bite indoors and outdoors
- Will take multiple blood meals
- Do not fly far: ~50m
Global map of the predicted distribution of *Ae. aegypti*. The map depicts the probability of occurrence (from 0 blue to 1 red) at a spatial resolution of 5 km × 5 km | Taken from Kraerner et al., (2015)
Aedes albopictus

- Less adapted to urban environment (sylvatic)
- Less aggressive biters
- Usually smaller populations
- Can survive in temperate regions
Global map of the predicted distribution of *Ae. albopictus*. The map depicts the probability of occurrence (from 0 blue to 1 red) at a spatial resolution of 5 km × 5 km | Taken from Kraemer et al., (2015)
Other vectors?

Anopheles
(malaria)

Aedes
(dengue, chikungunya, yellow fever)

Culex
(filariasis, West Nile virus)

Zika virus has been isolated from all three genera
Control?

- Insecticides (adults, larvae)
- Dissinsection
- Personal protection
- New tools – GM and wolbachia?
- But lack of efficacy... or evidence?

Bowman L, Donegan S, McCall PJ (2016) PLoS NTD
Aedes control – lack of efficacy or evidence?

960 studies since 1980

19 studies had data for meta-analysis. Only 9 were RCTs.

Many show reduction in vector populations, but what about transmission?

House screening is only intervention to show an effect for dengue

Given the lack of reliable evidence, standardised studies of higher quality, with epidemiological outcomes, must now be a priority

Bowman L, Donegan S, McCall PJ (2016) PLoS NTD
Repellents

1st line of defence
Recommendations

4 actives: DEET, PMD, Picaridin, IR3535

High risk: high levels of DEET (20%-50%)

Low risk: low levels of DEET (below 20%), icaridin or PMD

No risk: high levels of DEET not required. Use whatever safe natural alternative works for you
Can pregnant women use repellents?

Yes

Randomised, double-blind control trial in Thailand involving 897 pregnant women showed no adverse effects of DEET on participants or babies when followed for a year after birth.

No trials have assessed the safety of PMD, Icaridin or IR3535 in human pregnancy so product label directions should be followed.
Do repellents protect against disease?

<table>
<thead>
<tr>
<th>Country</th>
<th>Outcome</th>
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<tr>
<td>Afghanistan (Rowland et al. 2004)</td>
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<td>Bolivia (Hill et al. 2007)</td>
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<td>Ecuador &amp; Peru (Kroeger et al. 1997)</td>
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<td>India (Vittal and Limaye, 1984)</td>
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<td>Lao PDR (Chen-Hussey et al. 2013)</td>
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<td>Pakistan (Rowland et al. 2004)</td>
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<tr>
<td>Tanzania (Moore et al. 2011)</td>
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<tr>
<td>Thailand (McGready et al. 2001)</td>
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Meta-analysis

- 8 trials of repellent against malaria

- 4 with *adequately reported methods or data* for a meta-analysis

- Non-significant reduction of 30% in risk of *P. falciparum* infection

DEET risk assessment

• USEPA in 1998: study showed minor effects; at greatest exposure (1000mg/kg body weight/day) rats showed renal lesions and decreased body weight
  
  – Renal lesions were male specific and unique to rats, not to humans
  – Micropig study: same exposure showed no effect
  – Adverse effects so modest and dosage so high = no risk assessment was required

• Weigh up the risk of low repellent concentrations that are ineffective with risk of vector borne disease transmission

• Historic use of DEET and safety record...

Chen-Hussey V, Behrens R, Logan J G (2014) How safe is the insect repellent DEET? Parasites and Vectors
DEET safety?

- 1980s & 90s: 14 cases of seizures following DEET exposure in girls aged 1-8 years
- Widespread concern and reviews of DEET safety, however, **no causal link or mechanistic pathway was ever found**
- 9,000 calls to American Poison Control Centers (1993-1997)
  - 54% no symptoms
  - 6% had unrelated symptoms
  - 30% had mild symptoms treated at home
  - 10% referred to health care facility, but discharged after initial examination
  - 0.5% admitted to a health care facility
- Severe symptoms related to inhalation or eye contact

Chen-Hussey V, Behrens R, Logan J G (2014) How safe is the insect repellent DEET? *Parasites and Vectors*
Mosquitoes ignore repellent Deet after first exposure

By Rebecca Morelle
Science reporter, BBC World Service

The widely used insect repellent Deet appears to be losing its effectiveness against mosquitoes, scientists say.

Researchers from the London School of Hygiene and Tropical Medicine say mosquitoes are first deterred by the substance, but then later ignore it.

They say more research is needed to find alternatives to Deet, which was first developed by the US military.

The research was carried out on Aedes aegypti, Deet works the first time, but for some hours
Mosquitoes can be selected to become resistant to DEET

Does this mean we should stop using DEET? **NO!!!**

• Repellents are important

• One of few preventatives - particularly against Zika, dengue, chikungunya

• Recommended by international health organisations

• Must be mindful not to create barriers to product development
Comments on PT19 Guidance

What is needed?

• Standardisation

• Clarity

• Sound methodology & interpretation to inform better label claims

• Robust testing but “sensible” expectations
14.2 Dossier Requirements
(page 44)

- Refer to “established guidelines” – international, EU or national or WHO or own method (so long as scientifically robust)

- But a “semi”-protocol is given

- Clear guidelines for efficacy testing is necessary
Issues with longevity claims

- Variation between individuals

- Species *Culex vs. Aedes vs. Anopheles*

- Study design:
  - Exposure time
  - Number of mosquitoes
  - Cage size
  - Dosage
  - CPT or cut-off

- Clinicians do not give advice on the label...
Variation between individuals

• Repellents work differently on different people

• EU recommendation for number of participants: none

How do we take care of this?
  – More than one volunteer!
  – Calculate median protection time across all volunteers (with Kaplan-Meier Survival Function)
  – Sample size? Not clear

• EPA & WHOPES recommendation: enough for statistical analysis
  – EPA, median CPT calculated with Kaplan Meier Survival Function (non parametric analysis) or Mean CPT (normal distribution)
  – WHOPES median CPT calculated with Kaplan Meier Survival Function
Test Species
(Section 14.2.1; page 45)

• Current EU recommendation: *Culex* (Europe) and *Aedes* (aggressive); no mention of *Anopheles*

• WHOPES: recommend 3 genera

• EPA: *Ae. aegypti*, an *Anopheles* species or *Culex*

• Can label claims be made to reflect efficacy against particular species or region?

Our recommendation: all three genera
Factors that could affect efficacy/longevity:

- **Exposure time**
  - EU: 5 minutes
  - WHOPES: 3 minutes
  - EPA: no recommendation
  - Our recommendation: 30 secs Aedes and Anopheles; 1 minute for Culex

- **Number of mosquitoes**
  - EU: no recommendation (but reference to study in annex with 10 mosquitoes)
  - WHOPES: 200-250 (in 2 cages)
  - EPA: at least 200
  - Our recommendation: 50
• Cage size
  – EU: no recommendation
  – WHOPES: 35 x 35 x 35
  – EPA: 60 x 60 x60
  – Our recommendation: 30x30x30cm

• Dosage
  – EU: no recommendation
  – WHOPES: 1ml/600cm² forearm
  – EPA: 1g/600cm² forearm or typical consumer dose
Dosage?

- Standard 1ml/600cm$^2$ forearm is a large volume
  - Consumers unlikely to put this amount on in reality.

- Typical consumer dose? Not consistent

- Standardisation needed; perhaps lower than 1ml/600cm$^2$
End point: CPT or a certain % for cut-off?

EU (14.3.1 Norms and criteria, page 48)

“Products for use as repellent on skin or clothes:
  – During claimed protection period – protection should be ~100% (CPT)
  – If less, restrictions should be placed on products preventing marketing for prevention of disease transmission”

WHOPES: CPT

EPA: CPT
• Other current EU recommendations:

  – Record landing and probing
  – Or use rabbit
  – Or experimental hut
  – Arm-in-cage AND field trial

“14.2.3 Requirement per type of claim (page 47)

Products for use as repellent on skin or clothes:

  – Arm-in-cage
  – Field trial”