Main FR issues in the repellent dossiers for humans

• Isabelle ATTIG - Head of Efficacy unit
Repellent French dossiers evaluated until now

- Target organisms: mosquitoes, sandflies, ticks, lice and wasps (currently in evaluation)

- Repellents for humans (repellent for animals currently in evaluation)

- Mode of application: skin, textiles

- Active substances in the dossiers: DEET, IR3535, Lavender oil (low risk)

- A PT19 guidance available nevertheless methodology and criteria are not available for all target organisms
Repellent for mosquitoes are addressed in the chapter 14.2.2.3.4 with specific requirements and criteria in the chapters 14.2.3 and 14.3.1.

⇒ Simulated-use test as « arm in cage test »

⇒ Field tests: nevertheless, not required anymore following an e-consultation in 2012 where Efficacy group agreed about the robustness and sufficiency of arm in cage test.
<table>
<thead>
<tr>
<th>TNsG on PT 19</th>
<th>WHO method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure of forearm during 5 minutes (as EPA)</td>
<td>Exposure of forearm during 3 minutes</td>
</tr>
<tr>
<td>Not very clear: test repeated every hour but first confirmed bite within 30 min</td>
<td>Test repeated at 30-60 min intervals</td>
</tr>
<tr>
<td>(EPA: e.g. 30 minutes intervals)</td>
<td></td>
</tr>
<tr>
<td>Number of volunteers not indicated</td>
<td>Number of volunteers sufficient to allow for statistical analysis</td>
</tr>
<tr>
<td>(EPA: sample size should be justified statistically)</td>
<td></td>
</tr>
<tr>
<td>Untreated forearms of, preferably, the same test persons</td>
<td>Same forearm for the untreated and treated forearm</td>
</tr>
<tr>
<td>(EPA: 1 or 2 untreated control subject, positive controls included recommended)</td>
<td></td>
</tr>
<tr>
<td>Protection time: time between repellent application and time of 2 or more bites on the treated arm, or the first confirmed bite (a bite followed by another within 30 min)</td>
<td>Protection time: number of minutes elapsed between the time of repellent application and the first mosquito landing and/or probing.</td>
</tr>
<tr>
<td>(EPA: time from application until the first efficacy failure event confirmed within 30 minutes by a second similar event)</td>
<td></td>
</tr>
</tbody>
</table>
Discrepancies : TNsG, EPA and WHO method

- Exposure time => CA FR accepts 3 minutes instead of 5, as in the WHO method
- Interval of exposure : it seems relevant to repeat the test with a shorter interval (30 min instead of 1H) at the end of the protection time expected to frame it carefully :

<table>
<thead>
<tr>
<th>Interval of 30 min</th>
<th>Interval of 1 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6H30 : no land and/or bites</td>
<td>At 6H : no land and/or bites</td>
</tr>
<tr>
<td>At 7H : 2 lands</td>
<td>At 7H : 2 lands</td>
</tr>
<tr>
<td>At 7H30 : 3 bites</td>
<td>At 8H : 5 bites</td>
</tr>
<tr>
<td>Protection time of 6H30</td>
<td>Protection time of 6H</td>
</tr>
</tbody>
</table>

- Protection time : in France, time protection is defined as the number of minutes between repellent application and the first event (land or bites), confirmed by the second one.
FR issues from the dossiers

- Trials with a reference to a methodology not very precise, more a mix of references to TNsG, EPA and WHO method, notably for the criteria to define the time protection

- Few number of volunteers (often 3 with 3 replicates !) : e-consultation in 2012 to agree on the minimal number of 10 volunteers (and not 10 replicats !)

- Variability of the results between the volunteers (median CPT across all subjects have to be calculated statistically)

- Side effects on several volunteers in the efficacy test after application : discoloration, rush, redness
  How to deal with them if in the toxicological tests (not performed on humans), no adverse effect is shown ?

- Importance of the nature of the textile tested for application on clothes : most of the time only cotton is tested
FR issues from the dossiers

- The dose claimed on the label has to be tested on the arm-in-cage test, the dose is expressed in mg of product / cm² of skin

FR CA demands that this dose has to be expressed in a corresponding number of sprays on the label for the consumer

**Example**: the recommended application rate is 1.67 mg/cm² of skin
The ready-for-use spray bottle dispenses a spray dose of 1 g per spray. The number of spraying recommended is 6 per forearm (average 600 cm²).

⇒ The efficient dose is used in France for the risk assessment
FR issues from the dossiers

- Species tested: « tropical mosquitoes » claim is not accepted as not sufficiently precised regarding the situation of France: *Aedes albopictus* (Tiger mosquito) largely present in France, *Aedes aegypti* and *Anopheles spp.* present in overseas territories.

=> only species tested are stated in the label with protection time defined in the tests for each species.

Example:

<table>
<thead>
<tr>
<th>Label claims validated</th>
<th>Examples species tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culex spp : 8H protection time</td>
<td><em>Culex quiquefasciatus</em></td>
</tr>
<tr>
<td>Aedes spp : 7H protection time</td>
<td><em>Aedes aegypti</em></td>
</tr>
<tr>
<td>Anopheles : 7H protection time</td>
<td><em>Anopheles gambiae</em></td>
</tr>
</tbody>
</table>
Flaws in the methodology

The following flaws in the tests have conducted to reject the tests:

- Validity of the control according to WHO method: 10 landings in 30 sec on the forearms on the volunteers and not an additional volunteer only for the control.

- Presence of a treated sleeve around the area tested with several-fold the application rate: it biases the results and sur-estimates the efficacy.

- Conditions of temperature or humidity in the cage not representative (example 22°C instead of 27°C, 65% of humidity instead of 80%).

- Number of mosquitoes in the cage not sufficient: 80-100 instead of 200-250 in the WHO/EPA method.
Risk mitigation measures

Product authorised by France should have the following RMM:

**Conditions of use linked to efficacy assessment**
- Respect the recommended application doses.
- Retreat after water exposure without exceeding the maximal recommended application number.
- The label has to respect the recommended conditions of use and the biocidal products labelling guide.
- The use of the product with other biocidal products or sunscreen products concomitantly is not recommended.
- Protection time can be lowered by sweating, water wash off, rubbing, high temperature (>30°C), wind velocity, etc.
Ticks : Requirement of TNsG PT19

Repellent for ticks are addressed in the chapter 7.2.2.2 with specific criteria in the chapter 7.3.1

⇒ Simulated-use with application on humans (alternative methods with animals are possible)

⇒ Field tests : not required as the simulated-test is considered as a worst case

⇒ Criteria : ≥ 90 % repellence during the claimed efficacy period
FR issues from the dossiers

- Stage tested: the relevance of testing only nymphs for the application on humans? Indeed, nymphs have in general a higher susceptibility and adults can also attach to human skin.

- French overseas regions then the species *Hyalomma marginatum* should also be tested, with *Ixodes ricinus*.

- Sometimes mixed products for humans and animals with the same trials.
Problem of interpretation of the guidance criteria: Example of EPA guideline

- A tick is considered as repelled if:
  - It does not cross into the treated area.
  - It crawls into the treated area but immediately turns back or falls off.

- A tick is considered as not repelled if:
  - It crosses the boundary line at least 3 cm into the treated area within 3 minutes, and remains in the treated area for at least one minute.

How to consider a tick that crosses the boundary line but not at least 3 cm into the treated area within 3 minutes, and remains in the treated area for at least one minute.

The laboratory proposes to include this case in the “repelled ticks”, but we could consider that if a tick stays for at least one minute in a treated area, this tick could be considered as not repelled.

FR CA decided to follow completely the recommendation of the EPA guideline and so considers that a tick is repelled only if it does not cross into the treated area or it crawls into the treated area but immediately turns back or falls off.
Case of lice

Requirements and criteria not addressed in the PT19 guidance.

- Main issues are the following:

  => Species involved: the body louse (*P. humanus humanus*) and the head louse (*P. humanus capitis*)? Possible read across?

  => Tests and Criteria proposed:
  For each target species / developmental stage / support (tissue/hair) claimed:
  - a laboratory test showing 100% effectiveness
  - a semi-field / simulated use test or a field test showing 95% effectiveness

*Field or semi-field trials must be representative of the product's use; the amount of product applied for each sample should be indicated, as well as tissue type, hair type and length*

*It will also be stated if mortality was observed after exposure: insecticide against lice is medical devices in France*
Case of wasps

Repellent for wasps are addressed in the chapter 15.2.2.2 with specific requirements or criteria in the chapters 15.2.3 and 15.3.1

⇒ No agreed protocol available
⇒ Discussion necessary with CA and/or Efficacy WG to agree on a protocol:

Different proposals in France for field tests; currently in evaluation
For mosquitoes, the TNsG should be more precise concerning the methodology, criteria, to be consistent with the WHO and/or EPA methods, to avoid issues in mutual recognition.

Add requirements and criteria for other targets organisms / mode of application, concerning by repellent products (notably the repellent product applied in another way as surface application)
Thank you for your attention