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EVALUATION OF TOPICAL MOSQUITO REPELLENTS AND INTERPRETATION OF EFFICACY DATA: A SYSTEMATIC LITERATURE REVIEW

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Abstract Under the European Union Biocidal Products Regulation repellents are classified as biocides, and are subject to efficacy studies. To facilitate testing of repellents for product registration the EU has provided technical guidelines. The guidelines leave uncertainties as to how efficacy should be examined and how data may be evaluated in terms of label claim. The question is how do laboratory arm-in-cage bioassays relate to real conditions? We conducted a systematic literature review to examine published laboratory and field repellent studies that measured protection time against biting mosquitoes in humans with one of the four active ingredients: DEET, icaridin, citriodiol/PMD or EBAAP. Out of 871 publications identified with the search term mosquito repellents only nine studies met inclusion criteria. The data were insufficient to make a quantitative comparison between laboratory and field studies, which indicates the need for studies to support authorities in making evidence-based decisions on label claims for product registration.
Key words Travel medicine, European Union biocides regulation, Culicidae.

INTRODUCTION

Biting mosquitoes (Diptera, Culicidae) are important vectors of several diseases including malaria, filariasis and viral infections, including dengue, West-Nile or chikungunya, particularly in the tropical and subtropical regions but also increasingly in Europe as recent autochthonous cases of dengue and chikungunya show (Tomasello and Schlagenhauf, 2013).

Topical repellents for application on the skin provide good protection against mosquito bites. Under the European Union Biocidal Products Regulation (No 528/2012) repellents are classified as biocides, product type 19, and as such are subject to rigorous efficacy studies. In order to facilitate testing of formulated repellent products for product registration the European Union has also provided technical (draft) guidelines. The guidelines leave uncertainties as to how efficacy should be examined and how data from such studies may be evaluated in terms of label claim, that is, how protection time measured in laboratory studies compares to protection time under end-user conditions.

In an attempt to address comparability between laboratory tests and field application we carried out a systematic literature review following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) principles (Liverati et al., 2009). Our objective was to identify and compare data from laboratory and field efficacy studies in humans that report protection time of at least one of the four United States of America Environmental Protection Agency approved active ingredients

for topical repellents against mosquitoes (DEET, PMD, icaridin and EBAAP). Here, we report the results of the systematic literature review and give recommendations for future studies.

MATERIAL AND METHODS

The systematic literature review followed the principles outlined in PRISMA (Liverati et al., 2009). We queried five literature retrieval data bases (Table 1) with the search term "mosquito repellents" for publications between 1953, the discovery of DEET, and end of March 2013.

Table 1. Data bases included in the literature review

Data base	URL
Cochrane library	http://www.thecochranelibrary.com
ISI Web of Science	http://apps.webofknowledge.com
LILACS	http://lilacs.bvsalud.org
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
ScienceDirect	http://www.sciencedirect.com

We included only studies that met the following criteria: 1) The study reports on repellents against biting mosquitoes; 2) The repellents were tested in humans; 3) The tested repellents contained one of the following active ingredients: a. ethyl-butylacetylaminopropionate (EBAAP); b. hydroxyethyl isobutyl piperidine carboxylate (icaridin); c. *N,N*-diethyl-meta-toluamide (DEET); d. *para*-menthane-3,8-diol (PMD) or citriodiol. 4) The study reports the protection time, either complete protection or relative protection above definedthreshold, e.g. ≥95%.
Studies that did not mention the applied dosage, described mixtures of repellents and literature reviews without original data were excluded from the analysis.

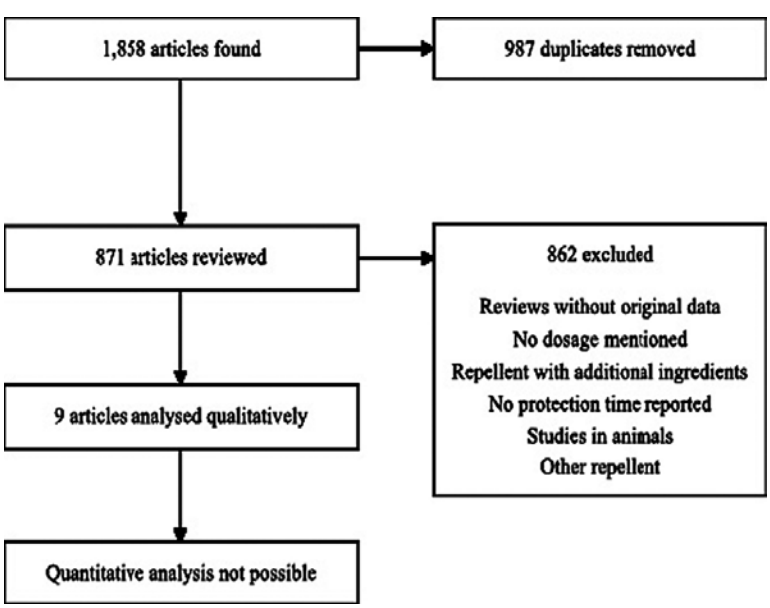

Figure 1. Selection process of available publications included in the systematic literature review.

RESULTS

After removing duplicates, the search term "mosquito repellents" yielded 871 unique hits yet only nine publications met our selection criteria (Figure 1).

In two out of the nine included publications, field and laboratory data were compared side-by-side (Carroll and Loye, 2006; Frances et al., 2009). From the remaining seven studies, one was a field study (Copeland et al., 1995) and six were performed under laboratory conditions (Ali et al., 2012; Barnard and Xue, 2004; Cilek et al., 2004; Drapeau et al., 2011; Logan et al., 2010; Obermayr et al., 2010). In addition of being only a total of nine publications, the formulations and concentrations, not even mentioning mosquito test species, varied widely across the studies (Table 2).

Table 2. Overview of studies included in the systematic literature review.

Repellent	Concentration (%)	Laboratory	Field
DEET	5	-	Copeland et al., 1995
	7	Barnard and Xue, 2004	-
	10	Carroll and Loye, 2006; Cilek et al., 2004; Logan et al., 2010	-
	15	Barnard and Xue, 2004	-
	20	Frances et al., 2009; Barnard and Xue, 2004; Cilek et al., 2004; Stanczyk et al., 2010	Frances et al., 2009; Carrol and Loye, 2006
	30	Carroll and Loye, 2006	-
	97	Ali et al., 2012; Drapeau et al., 2011	-
Icaridin	10	Barnard and Xue, 2004	-
	20	Obermayr et al., 2010	-
EBAAP	7.5	Barnard and Xue, 2004	-
	10	Cilek et al., 2004	-
	20	Cilek et al., 2004	
PMD	10	Carroll and Loye, 2006	-
	13	Drapeau et al., 2011	-
	20	Carroll and Loye, 2006; Drapeau et al., 2011	Carroll and Loye, 2006
	26	-	Carroll and Loye, 2006

In one of the two laboratory-field comparisons Frances et al. (2009) judged a 20% DEET against a 20% SS220 (a piperidine compound) formulation. The field study was done in Queensland, Australia. In their study DEET showed a longer protection against *Anopheles farauti, Aedes aegypti* and *Culex annulirostris* in the laboratory, while SS220 outperformed DEET under field conditions. In laboratory experiments the complete protection time of SS220 was between 18 and 180 minutes. DEET showed a complete protection time of 82 up to more than 360 minutes. However, the low sample size casts some doubts about the validity of the authors' conclusions. The study included only one and three human volunteers in the laboratory and field tests, respectively.

The other laboratory-field comparison (Carroll and Loye, 2006) measured protection time of DEET at 10% and 30% alongside PMD at 10% and 20%. Here, ten volunteers took part in the field study and even 24 volunteers were included in the laboratory study. DEET and PMD showed a similar efficacy against mosquitoes in the field- and laboratory experiments.
From the remaining studies it is also difficult to draw any conclusions. There was only a matching set of field and laboratory studies for 20% DEET (Table 2) and only for *Ae. aegypti* (The remainder of the studies listed in Table 2 and 20% DEET refer to other mosquito species prohibiting a fair comparison.) Intriguingly, for 20% DEET, Frances et al. (2009) measured a mean protection time of 195 minutes against *Ae. aegypti* in the field which is very close to the 180 minutes previously observed in the laboratory study by Cilek et al. (2004).

CONCLUSIONS

Though some studies suggest comparability between laboratory and field repellent studies, the resulting data were insufficient to make a quantitative comparison, highlighting the need for informative studies in order to support authorities in making evidence based decisions on label claims for product registration.

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