Proceedings of the Tenth International Conference on Urban Pests
Rubén Bueno-Marí, Tomas Montalvo, and Wm. H Robinson (editors) 2022
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CHALLENGES IN PLANNING AND EXECUTION OF EFFICACY FIELD TRIALS OF URBAN INSECT CONTROL PRODUCTS UNDER EUROPEAN BIOCIDAL PRODUCT REGULATION GUIDANCE

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Abstract In order to bring a new insecticide product to market in Europe there is a requirement to register it under the Biocidal Products Regulations (PT 18). One part of the process in granting a registration requires the submission and acceptance of a dossier that includes evidence demonstrating the efficacy of the product. The guidance notes offer means by which a submitted product may be tested to demonstrate compliance with the regulations. One term defined within this guidance is 'population control' which, when used in the context of defining efficacy of field trials for insecticides in the urban environments sets a hard limit of a population reduction of or exceeding 90% relative to either untreated sites or pre-treatment levels after a period of 2-10 weeks. The challenge of providing and executing useful and robust experimental designs under such circumstances against a backdrop of demanding customer expectations is discussed. The difficulties of running replicable field trials in urban pest environments is discussed and a case made for the increased acceptance of simulated use trials by competent authorities as a more robust way of demonstrating product efficacy under field conditions through the control of variables than undertaking trials on infested urban sites.

Key words: Insecticides, Registration, urban field trials

INTRODUCTION

EU regulation (EU) 528/2012 PT18 Biocidal Products Regulation (BPR) (European Commission, 2012) refers to Regulation concerning the placing on the market and use of biocidal products came into force on the 1st of September 2013. Two key requirements of BPR regulation is that all biocidal products require a registration by the European Chemicals Agency (ECHA) before they can be placed on authorised for sale by member states into the EU market, and that the active substances contained in the biocidal product have been previously approved (European Commission, 2012).

Product Type 18 relates to products to control arthropods including insecticides and acaricides by means other than attraction or repulsion specifically for pest control in the urban environment. The Technical Notes for Guidance for PT 18 includes the following:

"The following guidance is designed to be flexible and does not specify rigid protocols to which tests must be conducted. Published or unpublished data from any source will be considered provided the data are valid and relevant to the application." **(**European Chemicals Agency, 2018a)

'Flexible' is an unfortunately subjective term when considering the application of the BPR across EU member states and the concept of mutual recognition. Mutual recognition is as such:

"If a company wishes to extend the national product authorisation to other markets, it can ask other Member States to recognise it. Companies can apply for mutual recognition either in sequence or in parallel.

"To apply for mutual recognition in sequence, companies first need to get their product authorised in one Member State. After this, they can request other Member States to recognise this authorisation.

For mutual recognition in parallel, the company can submit an application for product authorisation in one Member State (called the reference Member State) and simultaneously ask other countries to recognise the authorisation as soon as it is granted." (European Chemicals Agency, 2018b)

There are a number of implicit assumptions in these statements: namely that the competent authorities of each EU member state is equally competent to assess a given product given climatic, social and economic variability; and that the degree of flexibility and pragmatism shown by one competent authority will be recognised by the another. Experience of preparing efficacy data for products to demonstrate efficacy over the past six years suggests these assumptions do not hold. The situation appears to have followed that expected by the 'Nash equilibrium' (Rapoport, 1966) end point state where the competent authorities least flexible in their approach to dossier submission will hold others to their own definition leading to the only agreeable state of flexibility being: none.

Field trials are being undertaken by Pest Management Professionals on customer premises against a background of increasing customer expectation and litigation by operators looking to select sites that will provide the best possibly of yielding results that will test the hypothesis being put forward as a claim.

The case is made here for a re-examination, not of the regulation itself which from the view of a private sector research scientist appears to be fit for purpose to the extent they interact with it, but of how it is interpreted by competent authorities in respect to field trial data dossier submissions for urban insecticides.

METHODS

The purpose of a field trial for a bait or residual application product is to test a hypothesis that said product, when applied in a field setting, will reliably provide 90% population control. The sampling unit is a population of target insects that are assigned to either a treatment or control group in order to test the claim of a causal relationship between the intervention with an insecticide and any change in population size from that of the control. A critical assumption is that the only cause of change in population could be down to the invention. Any asymmetry between populations violates this assumption. Equally, it is assumed that the only difference between populations is the randomised ascription as either treatment or control. As such, the populations must be discrete with no transfer of individuals (European Chemicals Agency, 2018a).

These assumptions are relatively easy to ensure in agricultural systems where field of monoculture crops represent a very symmetrical biological environment but pose significant challenges when applied to pest insects living in and around human structures. Furthermore, agricultural pests are qualified and quantified in status by their presence and number: this is absolutely not the case when considering urban insect pests. Urban pests may be classed as such based on features that are not directly measurable such as: risk of disease through acting as a mechanical or biological vector; risk of structural damage; indirect risk to health and sanitation; risk to livelihood and/or nuisance. The pest status of insects found around human habitations varies with a number of different factors including location, climate and the socio-economic level of the situation. Given these factors insects posing a potential risk to humans in an urban environment do so in a more direct way and at significantly lower population density (often in single figures). These factors, particularly risks of disease and threats to sanitation result make the identification and trial symmetry of control populations particularly challenging.

In summary, any method employed to quantify the efficacy of an insecticide intervention in the urban environment must be robust enough to provide replicable results on low populations of cryptic insects that potentially pose a threat to human wellbeing in settings that should factor in the presence of humans for the duration of the trial at different sites without compromising the essential assumptions of causality.

The need for demonstrable 90% mortality in order to satisfy efficacy requirements for a product dossier submission (European Chemicals Agency 2018a), limits experimental design options for urban insecticide field trials in as much as the requirement for an accurate measure of the initial populations of insects potentially subject to treatment is critical. Reliably gauging the absolute numbers of insects using methods that remove individuals from the small populations (adhesive traps or similar) can directly influence the population size, whilst being aware of but not removing insects when undertaking this work is often unacceptable to the owner of the trial site and might having legal implications for species that have a negative impact on human health. These limitations necessitate that a census be taken immediately prior to treatment at different location in parallel due to seasonal/climatic variation in population numbers, principally. Testing at the same location can often be desirable as long as the populations are discrete as only

one customer need be convinced that methods being employed to control pests on their site are worthwhile, particularly if the trial fails.

RESULTS AND DISCUSSION

Presenting the results of an idealised experiment such as that outlined above leads to a binary result: did the application of an insecticide (only) result in a mean 90% reduction in population size? The reduction of a complex ecosystem with many variables to a single simplistic outcome that does not take into account wider principles of integrated pest management in the urban environment is potentially why competent authorities appear reluctant to consider alternative means to evaluate product efficacy beyond this type of highly proscriptive type of trial.

The Technical Notes for Guidance are clear that:

"*In the case of field trials where true replication is almost certainly impossible to achieve and where normal control methods are not restricted to use of a single insecticidal product, a full description of any factor that might be expected to influence product performance should be given."* **(**European Chemicals Agency, 2018a)

With this is mind there is a strong case for a more widespread adoption of simulated use trial data being accepted in lieu of that that cannot be reasonably generated or feasibly, if ever, replicated by field trials undertaken at the point of submission or later by any other investigator. The above statement must be taken into account in the context of a 90% minimum efficacy requirement if that is being held as binary checkpoint of product approval, or else a field trial is not a viable means of product assessment.

The case for simulated use trials is then clear. Testing on a *definitively quantified* initial population of insects at comparable population density in low variation environments representative of field conditions would provide more robust results that are more easily tested in replication by subsequent investigators than site specific trials. This is especially relevant for products that are applied in micro-biomes within the wider urban pest environment.

There should be, for example, no difference in a flea treatment applied to a carpet kept at the same climate as a dwelling to one actually laid in one. The hypothesis of the experiment remains the same: "Given data to show that the application of the product results in sufficient mortality of fleas on a laboratory bench hold true when it is applied to a floor covering as it would be in the field?" The advantages being that a known number of fleas are counted in and counted out of the arenas for populations assigned to both intervention and control and any adverse human health effects experienced in the running of the trial can be factored into the design- particularly for those assigned to the control population.

If the definition being employed by Competent Authorities of flexible is, perversely, inflexible and guidance has indeed become rigid rule which must be followed, then is time to revisit them as their context has changed. Competent Authorities need the confidence to be flexible in order to keep efficacious products on the market rather than see them removed due to the difficulty and cost associated with proving it in the field (Adams, 2005). If the guidance is to remain unchanged then an equally inflexible definition of 'guidance' may be required.

ACKNOWLEDGEMENTS

Thanks are extended to Dawn Kirby, Senior Regulatory Manager at Rentokil-Initial PLC, for proofreading this manuscript before submission.

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