Introduction to development of internationally acceptable guidance principles for testing and deployment of GM mosquitoes

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Introduction

Genetically modified (GM) mosquitoes are currently being developed for use in vector control related to human diseases, such as malaria and dengue, under individual institutional or national guidelines on research and biosafety. There is a lack of directed international guidance, however, on the development, testing and ultimate deployment of such GM mosquitoes. In this current situation, uncertainty over what practices are widely acceptable may cause delay in technical progress, may deter some investment in the technology, and may cause some national regulators to demand diverse and irrelevant data or to impose excessive safeguards. There is also a possibility that experimentation could proceed with inadequate safety in some countries with weaker regulatory systems, under pressure to act in the face of rising impacts from disease. While we may look for lessons learned, guidance aimed at GM technologies in general – historically drafted in the context of GM crops intended for consumption – are not universally applicable to the particular technologies or circumstances of GM mosquitoes. The potential application of GM mosquito technologies across the wide range of disease endemic countries suggests that a broad consensus on the regulatory approaches taken at each stage of testing and deployment ultimately will reduce the burden on national resources and address concerns of cross-border effects from intentional release of living modified organisms. WHO/TDR has recognised this need and funds a project (MosqGuide, www.mosqguide.org.uk) to present best-practice guidance as a step in establishing this consensus.

MosqGuide has partners in Asia, Africa, Europe and Latin America working in consultation with national and international groups involved in technical development, testing and guidance on best practices or regulation. The project is designed in modules related to sequential stages of bringing GM mosquito technologies from laboratory to field. Module 1 provides an overview of current technologies and ethical, social and legal issues that must be addressed. Module 2 focuses on research and production issues. Module 3 concerns pre-deployment country decisions. Module 4 is about field release data handling and environmental monitoring. Module 5 comprises a pilot field study of public and regulator attitudes about alternative control methods, including GM technologies. Module 6 interfaces with capacity-building curricula. Finally, Module 7 is a prototype issues/response tool to support national or regional decision-making in disease endemic areas regarding deployment of GM mosquitoes.

What guidance, by whom?

Users of GM mosquito technologies would benefit from guidance, guidelines, or standards for the full range of activities needed to bring the technologies into use, such as: laboratory practices and cage trials; site selection for field trials and first open releases; production and transport of GM mosquitoes; and operational and environmental monitoring in deployment. Angulo and Gilna (2008) suggest three objectives (in the context of self-dispersing GM insects): consistent problem definition, analysis and decision making; minimal conditions for "wise use"; and compliance instruments.

Efficiency and understanding would be helped if common formats are adopted for risk analyses, and particularly for communication of risk regarding GM mosquito technologies. Such formats are agreed internationally in plant health, animal health and some areas of human health. Some detailed international standards exist now for similar scenarios, such as the release of biological control agents and other beneficial organisms (IPPC, 2005), confined field release of GM insects (NAPPO, 2007), and quality control and shipment of mass-reared sterile insects (FAO/IAEA/USDA, 2003). Although focusing on plant and animal pests, these provide useful cases of current, widely accepted approaches to the issues and models for the process of reaching agreement. The Organisation for Economic Cooperation and Development has recently published a guide on preparation of consensus documents related to biotechnology (OECD, 2008). There may be a need to provide a comprehensive set of internationally accepted biological information on the particular species and the technologies for GM mosquitoes.

Language to describe uncertainty and conclusions based on uncertainty has been carefully described by the Intergovernmental Panel on Climate Change (IPCC, 2005). This covers sources of uncertainty, the use of expert judgement, the precision and calibration of terms, and the quantification of confidence and likelihoods. National frameworks also provide useful examples. The Australia/New Zealand Risk Management Standard 4360 (Standards Australia, 2004) is helpful in providing guidance on consistent qualitative descriptions of likelihoods

and consequences in risk analysis. The New Zealand Environmental Risk Management Agency (www.ermanz.govt.nz) applies consistent procedures across the range of potential new organism introductions it judges. The Great Britain Non-Native Species Risk Analysis Panel (www.nonnativespecies.org) uses a model risk framework which translates into easily-communicated graphics for managers on risk and uncertainty.

The complexity of risks potentially posed by GM mosquito technologies makes it difficult to put responsibility for guidance onto a single agency. Concerns include both environmental and health impacts and apply to both the Convention on Biological Diversity (www.cbd.int), particularly through the Cartegena Protocol on Biosafety (www.cbd.int/biosafety/), and WHO (www.who.int). Intensive consideration by the CBD on the single issue of transboundary movement of GM organisms (CBD, 2006) indicated a need for broad coordination of many standard setting agencies, and this is also likely in a comprehensive approach to guidance on GM mosquitoes. In the end, however, decisions regarding risks must be taken in the context of possible health benefits.

Estimates on the cost of preparing technical, international standards in plant protection started at nearly US$200,000 for more conceptual standards (IPPC, 2007), with particularly controversial or complex standards costing up to US$3 million. A recent standard on a previously unaddressed issue (wood packaging material, ISPM 15) involved at least 1,700 man-days of effort to reach agreement among the approximately 170 contracting parties (IPPC, 2007). Attempts to agree on common understanding of Social Responsibility have taken nearly a decade and will result next year in a guidance document (ISO/CD 26000) from the International Organisation for Standardization (www.iso.org), one of the few standard setting bodies to require broader stakeholder inclusion.

Despite these costs, international guidance saves the burden of similar efforts on the level of individual countries, while allowing adaptation to national realities. Implementation of international guidance can require significant national documentation in support of testing, production and deployment of GM mosquitoes. This need not be costly for the countries involved, however. Fees for approval of introductions of GM organisms into containment in NZ, which has a fairly vigorous regulatory cost recovery policy, are approximately US$6,500 and for field testing US$23,000 (current fees from ERMA New Zealand,www.ermanz.govt.nz). The cost of documentation and hearings to applicants would be substantially greater than the regulatory fees.

Conclusion

The application of GM mosquito technologies would benefit from a comprehensive set of international guidance or standards. While there are precedents among current standards for similar processes, there are also divergent approaches which would need to be rationalised. The complexity of the issues involved suggests that guidance will need to be coordinated among a wide range of specialist technical and standard setting agencies, rather than emanating from a single agency. This may add to the time and cost of guidance and present conceptual differences in approaches to risk, but will save time and resources in the disease endemic countries where decisions on deployment ultimately will be made.

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WHO Technical Consultation on use of GM mosquitoes to inhibit disease transmission

Jim Lavery

Thoughts on relationships with host communities for caged and open field release trials

A central theme in the history of research involving human subjects is the concern that researchers will enlist or use individuals in order to answer scientific questions without adequate safeguards to ensure that their participation is both voluntary and reasonable in terms of any potential harms or potential benefits.

Although common in the history of anthropology and other social sciences, the concept of community engagement has been slow to find traction in the biomedical sciences. But as advances in genetic technologies made it possible, and increasingly efficient, to characterize whole subsets of a population as "at risk" for various types of cancer, or to be a particularly important reservoir for infectious disease, these communities have suffered very focused discrimination and stigma. The biomedical research community has been forced to re-think the ethical and social significance of interacting with communities in research.

Guidelines for the ethical conduct of research are evolving and have begun to reflect greater attention to the interests of communities and the corollary obligations of investigators and research sponsors. But even with this increasing interest, we have not yet developed adequate accounts of which community engagement practices are necessary, under what circumstances, and why.

Genetic and biologically modified mosquitoes raise a wide range of questions and concerns in communities in which caged field trials or open-release trials are being conducted or contemplated. At a fundamental level, it is not clear even what precise harms might befall communities as a result of hosting such trials. Similarly, although we have well-honed (though often questionably effective) procedures to limit harm for individuals engaged in research (e.g., informed consent), we are at the very early stages of determining what procedures might be most useful, effective, and appropriate for protecting communities participating in these trials, or even for gauging their willingness to participate in the first place.

My comments at the meeting will focus largely on our growing experience with community engagement in a wide variety of research contexts around the world and some preliminary thoughts about what might constitute effective community engagement in research involving modified mosquitoes. An initial framework for community engagement that a number of us developed and proposed as a starting place for community engagement activities related to caged field trials of GM mosquitoes in southern Mexico, has informed the continued evolution of the framework.

The key dimensions of the framework are (a) an explicit set of procedures or operating principles that provide a general architecture for how community enagement might be approached in practice (the rows of the framework); and (b) an explicit set of ethical commitments or principles that provide the underlying rationale for why various approaches might be considered "good" or "effective".

The framework itself is not the end product. Instead, it serves as an evolving "theory" of the effectiveness of community engagement and provides a convenient platform for collecting and analyzing a wide range of empirical insights from a range of research contexts, not limited to GM mosquitoes.

A key interest for our research group at the moment is how we might build partnerships to allow our emerging framework to serve as a "collaboratory", an open-source, interactive resource that will allow the on-going consolidation of insights about community engagement in global health in a way that will permit progress in our understanding.

Our ultimate aim is to develop an approach to community engagement that is equally valuable to investigators and communities and that lays out a shared set of commitments that can then serve as the basis for negotiations and specific decisions about initiating trials.

WHO meeting
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Geneva

Formulating an ecological risk assessment
David A. Andow

You will be hearing from the other speakers in this session of two contrasting approaches to ecological risk assessment of genetically engineered insects. These approaches may be useful models for some countries considering the introduction of GM mosquitoes, but other countries may find that their circumstances to be different. Hence there is a need to consider the ecological risk assessment (ERA) problem from general principles.

The most challenging aspect of ecological risk assessment is the formulation of problem. It is more of an art than a science. For GM mosquitoes, the main issue has been identifying potential harms or adverse effects on which to focus the ERA. Without this focus, one is left with a rather unsatisfying effort of trying to assess some kind of "average" effect on "biodiversity", which even if it could be measured well, is of questionable significance. In technical terms, this has been called a hazard assessment or a safety assessment.

Another challenging aspect of the problem is that almost no one likes mosquitoes. This creates a challenge because most people are willing to simply dismiss the possibility that harm could come from genetically changing or eliminating some of them. In addition, the diseases that they transmit are so devastating to human populations that we often simplify the problem to either them or us. But ecological systems are not Manichean. Species are not either good or bad; they are some blend, even when they are mosquitoes. In some ways, if we can address ecological risks of mosquitoes in the deft way demanded by ecological systems, then we will have a model for much less demanding introductions, be they exotic species or some other genetically engineered animal.

I have no easy suggestions.

The goal is to identify possible risk hypotheses. A risk hypothesis is a causal chain connecting a stressor to an endpoint. Here the stressor includes the processes of producing and releasing GM mosquitoes as well as the released mosquito itself. In other words, concomitant alterations of infrastructure and management should be considered in addition to the mosquito as a possible source of harm.

An assessment endpoint is a technical term, but to oversimplify a bit, it can be thought of as the bad thing that could happen. Change per se, it not bad. It is bad because the change runs against a social or cultural norm, or because a large group of people agree that it is bad. Bad is a reflection of human values. Consequently, in controversial cases, these values should be made clear, and the people who hew to them should be identified. As an aside, it is possible to introduce notions of environmental justice at this point.

For GM mosquitoes, there is one guidepost by which to organize the search for risk hypotheses. The kinds of possible adverse effects are known. These are adverse effects on biological diversity, adverse consequences of gene flow, and adverse environmentally mediated effects on human health. However, even this has not been that enlightening, because it is easy to get stuck simply repeating the category without being able to progress to specifics.

There are several ways to move to the specifics. Hayes et al. (2004, Env. Biosafe. Res. 3:109) illustrate a hierarchical holographic model. I will discuss two simpler approaches. The first is fault tree analysis. Fault tree analysis starts by listing all possible harms, whether they are caused by the stressor or not. The exercise is to work backwards up the causal chain, from the harm, and at each step inquire if it is possible that the stressor connects. Fault tree analysis comes hand-in-hand with event tree analysis, which starts with the stressor and tries to connect causal chains to a harm of any kind. Most of the published inquiry on the ecological risks of GM mosquitoes has implicitly taken the event tree approach.

To conduct a fault tree analysis, harms must be identified first. Sometimes we may lack the originality to imagine harms, and sometimes our imagination is overly fertile and there are too many to address. There are many ways to address the second possibility, using transparent, expert-driven, qualitative prioritization processes to limit the numbers. For GM mosquitoes, the first possibility seems more likely.

Another way to move to specifics is through a stakeholder process. I find the Mitchell et al. (1997, Acad. Manage. Rev. 22, 298) typology of stakeholders to be quite useful for thinking about selecting stakeholders. Once a group of stakeholders is identified, they can be asked to describe their environmental values. Within these descriptions are characterizations of harm. Fortunately this kind of work has already been initiated for GM mosquitoes, although it is called an ethical or social issue at this meeting.

If we can specify significant environmental harms, it will be possible to conduct fault tree analyses to generate possible risk hypotheses. The existence of a risk hypothesis does not imply that it is a significant causal pathway. Indeed, even a demonstrably significant pathway does not imply the risk is unacceptable. Although there is some distance between the risk hypothesis and a decision, without clear, specific risk hypotheses, a risk assessment is no better than watching leaves blow in the wind.