A RISK HIERARCHY FOR TRANSGENIC VECTOR ARTHROPODS

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Germline transformation has been achieved in an increasing number of arthropods and numerous applications are envisioned. Many of these organisms are vectors of human and animal disease and are being transformed for the purpose of interfering with their capacity to transmit disease. In spite of the intended beneficial endpoint of this effort, descriptions of measures for the safe creation and testing of these animals are necessary. Safe measures for purely laboratory studies have been addressed in the NIH Guidelines for Research Involving Recombinant DNA and the Arthropod Containment Guidelines, but neither of these addresses the conduct of contained field trials planned to occur before 2011.

In an effort to fill this gap in guidelines covering safe field trials of transgenic arthropod vectors, we developed a hierarchical classification of risk factors to consider for evaluating specific projects. This structure recognizes three features of transgenic arthropods that most prominently determine their risk classification: the intrinsic propagation potential of the transgene and its phenotype, the arthropod's sexual fertility status, and the specific phenotype conferred by the transgene.

The realm of commercial and large-scale applications of transgenic organisms consists of stable transgene insertions. Therefore, transgene mobility is a novel characteristic that warrants little concern. By contrast, one planned implementation of transgenic vectors is to inoculate populations with a relatively small number of transgenic organisms and to spread the transgene(s) into non-transgenic populations by various drive mechanisms. Therefore, to assess risk, mobility characteristics must be given special attention. This characteristic will strongly influence the expected variation in the transgene phenotype, and its mobility will produce mutations at insertions sites, both of whose characteristics must be understood clearly. We classify this characteristic – transgene propagation potential – as the first consideration.

The second characteristic, sexual fertility status, affects the probability that the geographic and temporal spread of the transgenic organism and its transgene can be controlled. Releases of sexually sterile transgenic organisms with short life spans and small migration distances will generally be of little long-term consequence. Conversely, release of fertile insects presents the possibility that the transgene may be vertically transmitted to progeny and the concomitant persistence and prevalence of the transgene increases the probability of and unanticipated effects and horizontal transfer.

The third consideration is the phenotype conferred by the transgene. We have assigned these four increasing levels of risk based on how intimately and directly they are expected to affect human health. The lowest level of risk is due to transgenes which contain only a marker. Examples of the application of such transgenes would be as markers for release/recapture and to study gene flow in natural populations. The second level contains transgenes that have an effect on the arthropods life history, for example

killing, sex ratio distortion, or life shortening. Third are transgenes that affect host-pathogen interactions. At the highest level of risk are those transgenes that directly affect human phenotypes. Only one proposal of this type has been described; antigen delivery in mosquito saliva to produce immunity to a pathogen.

TABLE: Relation of the Risk Classification Criteria. The lowest risk organisms are those with characteristics toward the upper left of the table, whereas those with the highest are toward the lower right. Each class is sequentially designated by its propagation potential, reproductive status, and phenotype e.g. 1-S-1 and 2-F-4 are the top left and bottom right classes respectively.

Transgene propagation potential	Vector reproductive status	Phenotype			
		marker only	vector population reduction	disease transmission reduction via non-human route	direct affect on human phenotype
1. Not significant	S-Sterile	1	2	3	4
	F-Fertile	1	2	3	4
2. Significant	S-Sterile	1	2	3	4
	F-Fertile	1	2	3	4