MADELEINE P. BALL

Regulate gene editing in wild animals

The use of genome-modification tools in wild species must be properly governed to avoid irreversible damage to ecosystems, says **Jeantine Lunshof**.

Gene editing is a hot topic following a flurry of interest in the use of CRISPR tools to modify human embryos. As an ethicist in a genome-engineering lab, I am an eyewitness to these recent scientific developments and I do have concerns about the way gene editing could be used. But they are not the concerns you might expect.

The ethical issues raised by human germline engineering are not new. They deserve consideration, but outcry over designer babies and precision gene therapy should not blind us to a much more pressing problem: the increasing use of CRISPR to edit the genomes of wild animal populations. Unless properly regulated and contained, this research has the potential to rapidly alter ecosystems in irreversible and damaging ways.

Scientists have already used CRISPR to modify mosquitoes and the fruit fly *Drosophila melanogaster*. And in combination with another molecular-biology technique called gene drive, they have found a way to massively increase the efficiency of spreading these transformations to offspring and through the population. Once introduced, these genetic changes are self-propagating. If released beyond the laboratory, the effects would spread with every new generation and would quickly run out of control.

Gene drive achieves rapid changes in a sexually reproducing population because it relies on genes that are capable of preferential spread through generations. Without this, introduced traits meet the statistical obstacle of Mendelian inheritance and take hold in a population much more slowly. Altering wild animal populations using gene drive aims to rapidly disrupt a particular trait, such as the ability of *Anopheles* mosquitoes to transmit malaria. It makes only a small-scale initial change to the relevant ecosystem and, in this example, the preliminary disruption would be restricted to the mosquito's natural habitat. But the risk of broader ecosystem disruption is unknown and would require extensive mathematical modelling to estimate.

The gene-drive technique was developed in our lab, and in the initial publication of the method, my colleagues called for strict and validated biosafety measures and public review and consent (K. M. Esvelt *et al. eLife* **3,** e03401; 2015). Meanwhile, work that combines CRISPR and gene-drive techniques is marching on. In what they call a "mutagenic chain reaction", scientists at the University of California, San Diego, have used the combined approach to alter *D. melanogaster* (V. M. Gantz and E. Bier *Science* **348,** 442–444; 2015). To me and others, this research raises serious and significant fears about biosafety. The work was done in a lab, but should any of the modified insects escape, they would be able to spread widely — unlike mosquitoes, which rely on ecological niches — and breed with the wild population. Experiments such as these should certainly be allowed, but only under the strictest conditions and with appropriate safeguards.

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In less than three years, CRISPR has become a key tool for biologists. 'Should they stop before it is too late?' is therefore an immaterial question. Careful assessment of the various applications of CRISPR shows that there is no single or universal ethical evaluation that could cover all of them. The different consequences of human genome modification in either somatic cells or the germ line, and the modification of the ecosystem through gene drives, call for different ethical and policy evaluations.

Some critics argue that the unpredictable effects that human germline genome editing could have on future generations make it dangerous and ethically unacceptable. Uncertainty, however, is not a useful way to judge ethical acceptability. Others highlight the potential non-therapeutic purposes of germline modification. From the standpoint of ethics, it is not clear why trait modification is by definition a bad thing. Moreover, the criteria for what is therapy and what is 'enhancement' are fluid.

WE NEED AN URGENT REVIEW OF BIOSAFETY PROTOCOLS FOR CRISPR AND GENE-DRIVE EXPERIMENTS IN WILD ORGANISMS.

The consequences of modifying human genomes will be limited because effects will always be restricted to humans — the index person and their line of descendants. Biosafety and biosecurity risks are not apparent at this moment. Regulation, if and when it comes, might need to be adapted to the local situation, to existing legislation and to cultural and religious normative frameworks.

Presented in those terms, the human applications of CRISPR are much less troubling than the possibility of ecosystem modification. By definition, such disruption has more severe, complex, system-level consequences, and the breadth of its impact and the duration of its effects are hard to model. Gene drives are designed to be reversible, but this still needs to be tested. Self-propagating modified organisms cannot be contained within national borders and pose major challenges for regulation and governance. We therefore need an urgent review of biosafety and biosecurity protocols for experiments — both in the lab and in field-scale trials — that combine CRISPR and gene-drive techniques in wild organisms. Funders and institutions must lay out and enforce regulations.

The work with gene editing has thrown a useful spotlight on these bioengineering tools. But from an ethical perspective, the question we should ask is not what CRISPR can do for humans, but what humans can do with CRISPR. ■

Jeantine Lunshof *is assistant professor at the University of Groningen, the Netherlands, and a visiting scientist at Harvard Medical School, Boston, Massachusetts, USA.*
e-mail: jelunshof@genetics.med.harvard.edu