REVIEW

Wicked evolution: Can we address the sociobiological dilemma of pesticide resistance?

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Resistance to insecticides and herbicides has cost billions of U.S. dollars in the agricultural sector and could result in millions of lives lost to insect-vectored diseases. We mostly continue to use pesticides as if resistance is a temporary issue that will be addressed by commercialization of new pesticides with novel modes of action. However, current evidence suggests that insect and weed evolution may outstrip our ability to replace outmoded chemicals and other control mechanisms. To avoid this outcome, we must address the mix of ecological, genetic, economic, and sociopolitical factors that prevent implementation of sustainable pest management practices. We offer an ambitious proposition.

The first documentation of resistance evolving to an insecticide was published in 1914, and the researcher who discovered the problem emphasized that if we did not develop approaches for more judicious use of insecticides, the problem of resistant pests would continue (*1*). Although agriculturalists have developed the field of "resistance management," with more than 3000 publications since 1980 (*2*), we mostly continue to use insecticides and herbicides (hereafter collectively called pesticides) as if resistance is a temporary issue that will be solved by commercialization of new products with novel modes of action (*3*). Evolution of resistance by arthropods and weeds to control measures costs billions of U.S. dollars per year (*4*, *5*) and may lead to loss of millions of lives (*6*). Breakthroughs in chemistry and molecular biology may provide many new pesticides and novel methods for pest control, but there is also a considerable chance that the evolution of pest resistance will outpace human innovation.

Consider the case of malaria, where the use of insecticide-treated bednets (ITNs) and indoor residual sprays (IRS) is estimated to have averted more than 0.5 billion cases of malaria between 2000 and 2015 (*7*). Resistance is evolving to the insecticides used, and there is growing concern over resurgence of the malaria-vector mosquito populations (*6*). Although efforts are being made to develop new insecticides aimed at mosquitoes (*8*), it is not clear that the new compounds will become available soon enough and be as cost-effective as the current ones.

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In 1996, companies commercialized genetically engineered crops that were not harmed by glyphosate, an herbicide that has broad-spectrum toxicity to weed species. The flexibility and profits that these crops brought to farmers resulted in over 90% of U.S. maize (corn), soybean, and cotton hectares planted to herbicide-tolerant varieties by 2014 (*9*). The accompanying widespread use of glyphosate resulted in more than 40 weed species evolving resistance and consequently diminished the utility of the herbicide-tolerant crop varieties (*10*) (Fig. 1, left). To address this problem, companies have reengineered crops to be tolerant of the plant hormone (auxin)–mimicking herbicides 2,4-D and Dicamba. These herbicides were first commercialized in 1945 and 1967, respectively. This reaching back to the past has become necessary because no herbicides with new modes of action have been commercialized in more than 30 years (*11*). Weed species have evolved resistance to every herbicide class in use (Fig. 1, right), and more than 550 arthropod species have resistance to at least one insecticide (Fig. 2). Cases have emerged where no pesticide remains effective. In Australia, weeds in wheat became resistant to all herbicides available and resulted in farmers designing machines to harvest weed seeds for population suppression [e.g., *12*].

If we are to address this recalcitrant issue of pesticide resistance, we must treat it as a "wicked problem," in the sense that there are social, economic, and biological uncertainties and complexities interacting in ways that decrease incentives for actions aimed at mitigation. Here, we summarize the interacting factors and conclude with a call for government support of ambitious landscape-level experiments to assess which pesticide use strategies decrease resistance risks.

Ecology and genetics

Insecticides and herbicides are typically designed to disrupt or mimic a single biologically active protein that is critical to survival of a pest organism. Protein targets in insects are typically involved in function of the nervous system, but some more recently developed insecticides affect growth and development. Herbicides often target enzymes involved in photosynthesis or growth patterns.

Resistance can emerge from a single mutation making a protein less susceptible to action of the pesticide. Alternatively, a single mutation can increase the amount or efficiency of an enzyme that degrades the insecticide or herbicide. These two modes of resistance are common (*13*, *14*), but other forms of resistance have been found that involve gene duplication or multiple genes acting together, each with a small but additive impact on resistance (*15*).

One or two locus population genetic models permit a general understanding of pesticide resistance evolution. More realistic, predictive models require combining population genetics with empirical data on population biology (e.g., life history, mating behavior, and gene flow) of the pest species and the fitness of each genotype in environments with and without the pesticide (i.e., fitness cost). Accurate data on these parameters are difficult to collect and can vary among localities. Most insecticides are sprayed at a specific concentration on a given crop, but over time the insecticide decays, so insects contacting a sprayed plant 1 day versus 10 days after the spraying encounter different doses. The dose on day 1 might kill 90% of insects homozygous for the susceptible allele and only 10% of those homozygous for the resistant allele, while on day 10, only 20% of the susceptible homozygotes would die. If most of the insects were encountering the insecticide-treated plant on day 1, the rate of resistance evolution would be predicted to be faster than if most of the encounters were on day 10. To further complicate matters with insecticides and herbicides, not every sprayed plant or plant leaf receives the same amount of pesticide. In sexually reproducing weeds and insects, the rate of resistance evolution is strongly influenced by the relative fitness (dominant to recessive) of heterozygotes, and this sometimes depends on the dose of pesticide encountered in the field (Fig. 3). Thus, it is difficult (and controversial) to determine whether resistance is expected to evolve more rapidly to higher or lower application concentrations of a pesticide [e.g., *16*, *17*].

Even more complexity arises in attempts to predict resistance evolution when combinations of pesticides are applied (*18*, *19*). Although the idea that such combinations will slow resistance evolution is theoretically controversial and lacks empirical support, mixtures are often recommended at the field level (*15*).

Although there is high uncertainty regarding many resistance management choices, under almost all circumstances entomologists agree that using an integrated pest management (IPM) approach that results in fewer insecticide applications should decrease the rate of resistance evolution (*18*).

Toxins derived from the bacterium *Bacillus thuringiensis* (Bt) have been widely used in engineered insecticidal crops. Here, variation in the dose of toxin received by insects is less of a problem (*20*). Engineered plants can produce season-long Bt-toxin concentrations that, for some insect pests, kill all susceptible individuals and almost all heterozygotes (*21*). Season-long consistently high toxin doses, when coupled with a percentage of the crop planted to a nontoxic variety (i.e., that act as refuges for susceptibility) is predicted to slow resistance evolution by a factor of 10 to 100. This strategy is known as the high-dose/refuge approach (*17*) and has been used for more than 20 years with some target pests. Tabashnik and Carrière (*22*) have examined 30 cases of long-term planting of Bt-toxin–producing crops: In nine cases where a high dose of Bt was achieved, neither economically important target pest resistance nor early warnings of resistance were found, but in 17 of 21 cases in which high doses were not achieved, resistance had evolved or showed evidence of emergence. Some of the cases of resistance occurred in low- or middle-income nations where refuges were not planted or where the crop varieties were not engineered for the relative susceptibility of the local pests and therefore did not maintain a high enough toxin dose.

The focus in the resistance management literature is on resistance to chemical control, but widespread use of other control tactics—including biological control, crop rotation, and hand weeding—also faces the challenges of resistance evolution (*23*). For example, the northern and western corn rootworms, which are mostly restricted to feeding on maize (corn) roots as larvae, have evolved resistance to the rotation of maize and soybean. One species has evolved to mostly overwinter as an egg for 2 years instead of 1, so when there is a typical 2-year rotation of maize and soybean, the larvae emerge from the hatching eggs in time for the next maize planting. The other species evolved to lay some of its eggs in the soil beneath soybean plants, "anticipating" maize in the next season. Most amazingly, some weeds have evolved to look like rice plants and thus avoid hand hoeing, and others have evolved seeds that mimic those of the crop they infest and are replanted along with crop seeds (*23*).

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Whenever humans act in any way to decrease the fitness of an insect or weed, natural selection is likely to result in a response. Insect growth regulators that mimic hormones were at one time considered resistance-proof insecticides, but in the end this tactic did not deter evolution of resistance (*23*). Ultimately, even with all of the biological uncertainties involved in resistance management, it remains the only current option for limiting the economic and social impact of pest evolution.

Economic perspectives

Pesticide resistance has both economic causes and economic consequences. Agricultural benefits lost from resistance in the United States have been estimated at about US$10 billion per year (*5*). Globally, reliance on pesticides has been increasing (*24*), exacerbating the impact of resistance. Pesticides also bear costs for the environment and public health (*24*). Some pesticides, such as Bt toxins (used either in engineered crops or in organic agriculture), have replaced broader-spectrum pesticides that were more toxic to nontarget organisms (*24*). Hence, a loss in the effectiveness of Bt toxins owing to resistance has environmental consequences if we revert to a less target-specific replacement. This rationale has been used in the formulation of government regulations for managing resistance to Bt crops (*17*).

Insecticide resistance in public health is also imposing substantial damages, although fewer studies are available that quantify the economic costs. Model-based analysis has shown that if disease vector resistance to pyrethroids becomes widespread, cases of malaria averted with ITNs could decline by 40% (*25*). Coupled with the estimate that bednets averted more than 65 million clinical malaria cases in sub-Saharan Africa in 2015 (*7*), and assuming that this figure provides a lower bound for potential cases averted in subsequent years, this would imply around 26 million additional clinical cases of malaria per year as a result of widespread vector resistance. Assuming an approximate lower bound cost of illness of at least $10 per malaria episode (*26*), insecticide resistance could

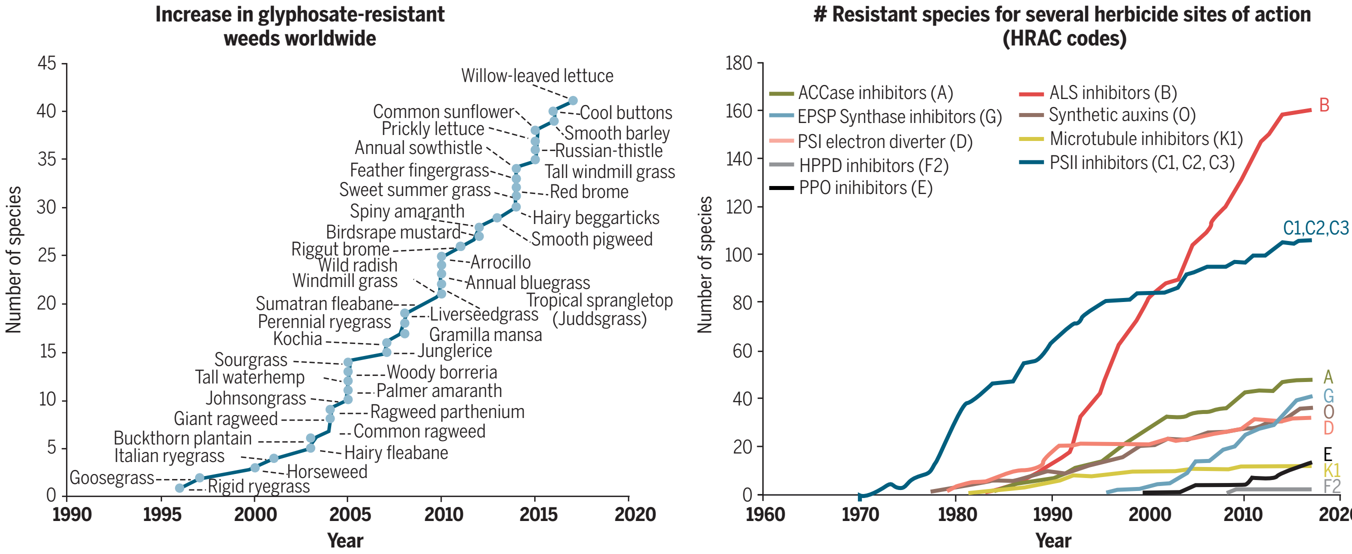

Fig. 1. Weed species with resistance to herbicides. (**Left**) Cumulative number of weed species with resistance to glyphosate. (**Right**) Cumulative number of weed species with resistance to herbicides in the major mechanism of action groupings.

CREDIT: I. HEAP, WEEDSCIENCE.ORG 2018, ADAPTED BY H. BISHOP conservatively cost sub-Saharan Africa at least $260 million per year.

Although these numbers make clear that the potential costs are large enough to warrant stronger policies for managing pesticide resistance, they do not tell us exactly what return society might expect from different investments in resistance management. The most basic insight from economics is that efficient pesticide use should weigh current net benefits of use against the costs of lost future effectiveness (*27*). To assess these future costs, economic discounting and the uncertainty of developing replacement pest control technologies must be factored in. As yet, the user costs of resistance are not computed in any systematic way, although recent methods for computing prices for natural capital and ecosystem services could be applied (*28*).

Laxminarayan and Simpson (*29*) have analyzed the optimal refuge sizes for managing pest resistance to Bt crops. They found that fitness costs of resistance are critical for determining whether refuges are economically efficient in the long run. Fitness costs determine whether susceptibility can be renewed after accumulating high levels of resistance in the pest population. If this renewal rate is less than an expected rate of return on financial assets, then it is optimal in the long run to deplete pesticide susceptibility. Likewise, the importance of fitness costs has shown for economic management of resistance to pyrethroid insecticides in malaria control (*30*) and agriculture (*31*).

Fitness costs, dominance, and initial frequencies of resistance genes remain highly uncertain in field settings for many pesticides. However, reducing uncertainty is costly, and better information may be more actionable for some of these factors than others, as has been shown for malaria vectors (*32*). For example, more certainty about the efficacy of noninsecticidal alternatives may be more valuable than better information about the fitness costs of resistance.

Ultimately, the costs of pesticide resistance to users depend on available control alternatives. However, no herbicides with new modes of action have been commercialized in more than 30 years, and the estimated cost of discovery of new insecticides has increased by a factor of eight in the past 50 years (*33*). Other tools with demonstrated effectiveness at managing resistance within an IPM framework range from biocontrol (*34*) to the sterile insect technique (*35*), but the implementation of these approaches is costly and complicated.

Pesticide susceptibility shares properties of a common pool resource (*36*). One party's use of a pesticide draws down the stock of susceptibility to that pesticide available not only to that party but also to other users. Furthermore, one user cannot limit use of the stock by others. The result is that users overexploit the resource relative to what would be economically efficient. One solution is to tax pesticide use to reflect the marginal user costs of resistance and the negative environmental impacts of pesticides. Four European countries have implemented pesticide taxes based on these motivations, although practical challenges impede their broader adoption (*37*).

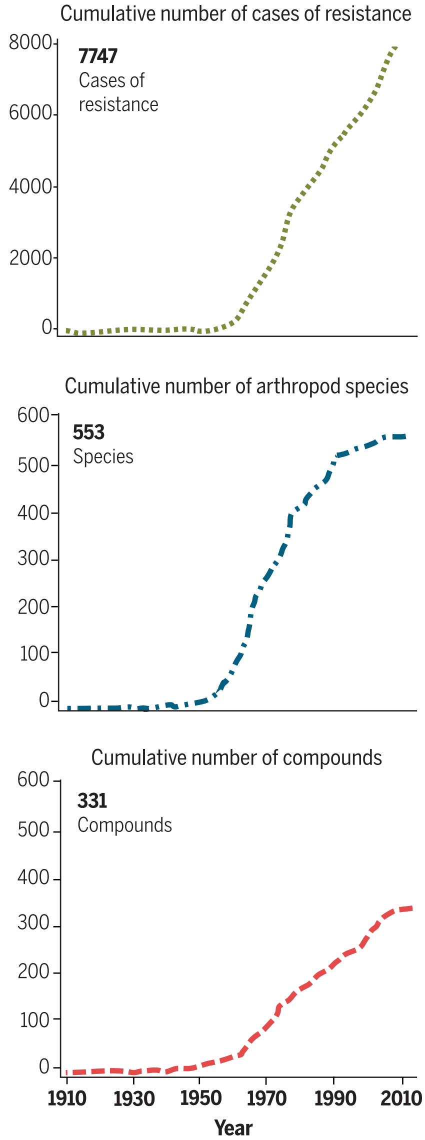

Fig. 2. Arthropods with resistance to insecticides. Data from 1910 to 2010 showing total number of species (dark blue dotted and dashed line), total number of cases of resistance to any insecticidal compound reported from a new location (green dashed line), and total number of compounds with resistance found in at least one arthropod species (light blue dashed line) (*56*).

One rationale supporting the laissez-faire management of weed resistance to glyphosate was the erroneous assumption that weeds were relatively immobile (*3*). This contrasts with extensive regulation of Bt crops to manage insect resistance, where the mobility of target pests of Bt crops was explicitly used as one rationale in refuge policies (*17*).

Because the use of Bt crops and other control tactics can result in suppression of the target pest over wide areas, incentives for overexploitation of susceptibility can be counterbalanced by the public good of areawide pest suppression. For example, areawide suppression of the European corn borer in the U.S. Midwest from use of Bt maize reduced pest damages by $2.4 billion among growers of non-Bt maize (*38*). Subsequent modeling shows that this areawide protection incentivizes planting of non-Bt varieties (*39*), which is predicted to slow resistance evolution further.

Sociopolitical perspectives

Efforts to decrease the uncertainties of pest resistance are critical to effective management, but an understanding of how these aspects intersect with social and political factors is also needed. Currently, the emphasis is on educational and incentive programs. However, these have not substantially improved resistance management and, as Ervin and Jussaume explain, "often fail to take into account the fact that farm-level decision-making takes place within complex social-cultural settings" (*40*). Sociopolitical research in this area applies at the level of the individual (micro level), the community (meso level), and the federal government or nation-state (macro level). Sociopolitical approaches have rarely been applied to resistance management, so concepts and examples must be drawn from other settings.

Individual level

The individual level of decision-making about pesticide use and resistance management mostly resides with farmers. In public health, households are often the key micro-level decision-makers, as in the case of whether or how to use a bednet. Most research on individuals' perceptions and decisions about pesticide use is framed around economic models of demand for pest control and risk reduction (*41*, *42*) and does not specifically address resistance. Resistance management could benefit from risk perception studies that have been used to analyze other technologies. Such studies would shed light on how factors associated with (i) technological options (e.g., controllability and familiarity), (ii) individuals themselves (e.g., culture, demographics, and worldviews), or (iii) risk managers and communicators (e.g., level of trust and perceived fairness) influence people's perception of risk and motivate them to take action for reducing resistance.

Community level

At the community level, social systems can support or interfere with resistance management programs and compliance. Social capital has been correlated with positive effects on IPM and sustainability, especially in developing nations (*43*). Research on network ties and social capital among U.S. farmers, and their relationship

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to the successful implementation of resistance management programs, could shed light on how to enhance collective action.

Because pest susceptibility can often be considered a common pool resource, Ostrom's work on the governance of such resources suggests that resistance may sometimes be better managed by on-the-ground, networked communities generating their own rules and norms for pesticide use (*44*) than by more formal, top-down governance. Regional programs, such as weed management areas, in which local farmers vote to implement different resistance management strategies (*40*), fit this model. In another example, pink bollworm resistance to Bt cotton in the southwest United States has been effectively delayed through voluntary cooperative initiatives and cost-sharing between regional grower associations and the U.S. Department of Agriculture (*35*). In terms of management tools, policy process frameworks, such as institutional analysis and development, can inform the design, implementation, and evaluation of common pool resource governance systems (*44*, *45*). Behavioral tools, such as social marketing, to engender norms for resistance management have also shown recent promise (*46*), but further research is needed.

Macro level

Systems theory and thinking at the macro level can help to uncover the underlying factors contributing to policy problems, such as resistance management, by taking complexity and multiple types of competing and intersecting forces into account (*47*). In complex situations, quite often the most intuitive policies have immediate benefits but over time exhibit counterintuitive behavior (i.e., policy resistance) and fail owing to unanticipated feedback (*48*). For example, the price of maize rose in the first decade of the 21st century in large part due to ethanol mandates in midwestern states, as well as subsidies and higher oil prices. This led to a near-term economic advantage for farmers who stopped rotating maize with soybeans and instead planted maize continuously (*49*). The continuous planting of Bt maize could have led to higher pest resistance to Bt in those areas, an issue that requires further investigation.

Political economy studies at the macro level can also uncover underlying tensions and barriers to effective solutions. For example, chemical companies will desire to sell more

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pesticides and increase short-term company profits. Sales tactics will compete with government regulators' desires to contain pesticide use to mitigate health and environmental risk. However, recognizing the need to protect the efficacy of their products over the long term, some biotechnology companies selling Bt crop seed have partnered with federal agencies and farmers to implement resistance management programs. For instance, the selling of seed bags with a mixture of Bt and non-Bt seeds allows companies to maintain their level of product sales while complying with regulatory guidelines. It also improves compliance by farmers, although it decreases a farmer's ability to control the situation and might therefore increase their perception of risk and decrease trust at the micro level.

National research policy affects how much knowledge and data we have on all of the factors relating to pest resistance and management. Gaps in biological and economic research are affected by the national priorities of each political administration but have traditionally been underresourced, despite their importance to the growing challenge of resistance management (*50*).

A way forward?

We have seen how pesticide resistance is a "wicked problem" arising from interacting uncertainties and competing interests that decrease incentives for action. A pessimistic conclusion would be that the status quo of little action will hold until a major crisis arises. A more proactive stance is challenging but likely to be less costly in the long run, so we conclude by suggesting two optimistic ways forward.

First, in the case of engineered insecticidal crops, a natural experiment has already been performed, and we know with some certainty what action needs to be taken to develop high-dose/refuge approaches that when tailored to specific systems will slow resistance evolution. Still, we must overcome competing interests that hinder our ability to build the political will on the part of governments to work with companies and farmers to ensure appropriate development and use. As observed by Foley (*51*), "GMOs [genetically modified organisms] have

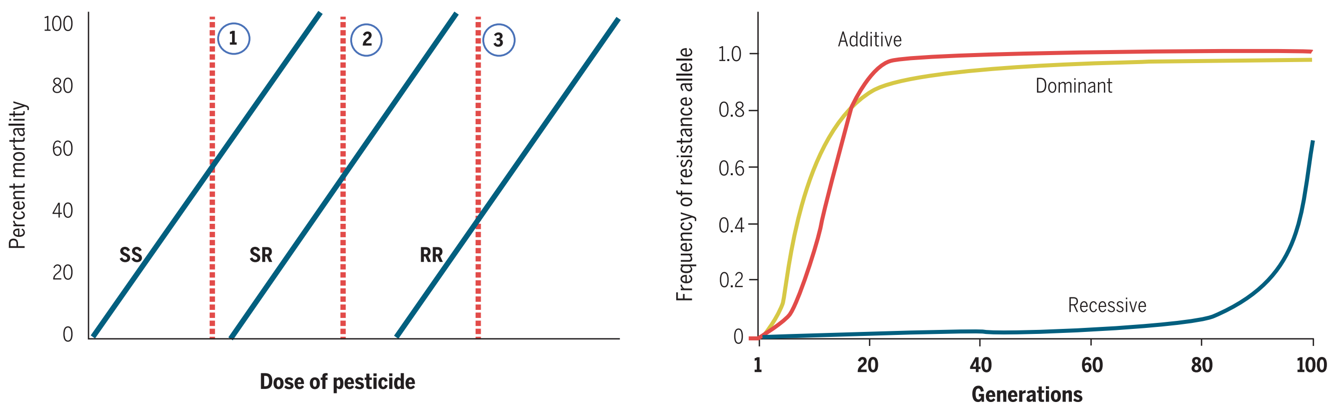

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Fig. 3. Response to selection for resistance to toxins. (**Left**) The solid dark blue lines show the generally expected relationship between the dose of toxin and the mortality of pests that are homozygous for susceptibility alleles (SS), heterozygous (RS), and homozygous for resistance (RR). The vertical, dashed red lines (numbered 1, 2, and 3) show the expected mortality of the three genotypes at different toxin doses. At dose 1, the RS and RR individuals similarly have no mortality, whereas the SS individuals have 50% mortality, so the resistance trait is dominant. At dose 2, the RS mortality is intermediate between SS and RR, so resistance is additive. At dose 3, there is 100% mortality of SS and RS and only 30% mortality of RR, so resistance is recessive. (**Right**) Trajectories of increase over time in resistance allele frequency when resistance is dominant, additive, and recessive.

frequently failed to live up to their potential, not because they are inherently flawed, but because they have been deployed poorly into the complex social and environmental contexts of the real world." Governments should insist on feasible plans for strict enforcement of appropriate use as a condition for commercialization. Knowledge from the social and natural sciences will be needed to guide such governance.

The second and more complex challenge to tackle is for conventional pesticides where there is still a high degree of uncertainty about what the best approaches are to stymie resistance. Although we have data from small-scale experiments, these are not sufficient for understanding resistance dynamics at a landscape level. For crop insects and weeds, large-scale, experimental agriculture, coupled with technical innovation, must go hand in hand. New breakthroughs in genomics and bioinformatics are providing tools that enable detection of genomic responses of insects and weeds to selection with pesticides [e.g., (*52*)]. These tools will put us in a good position to conduct landscape-level experiments on the order of thousands of hectares to decrease uncertainty about the effectiveness of various resistance management practices. It should be possible to detect early genomic and biological signs of resistance and to change management practices before resistance becomes an economic problem. Although these measures will be expensive, complex experiments even with the most localized pests, similar, large-scale endeavors have been tried for eradication of specific insects and weeds, so some of the groundwork has been laid. In addition, such studies will require input from the social sciences to gain appropriate community involvement. Although large-scale experimentation is a substantial investment, in the United States the cost to the federal government (i.e., to taxpayers) for crop insurance to cover crop failures in 2011 was estimated at more than $11 billion, with 265 million acres enrolled (*53*). Policies are being pursued to encourage other agricultural practices, such as cover crops for soil conservation, by tying cover-crop planting to discounts on crop insurance premiums (*54*). Similar approaches could be used for pesticide resistance management. The United States is not the only country with crop subsidies. Certainly, there is a way to use these public investments for the public good of avoiding the long-term costs of resistance.

The United States is about to begin a huge experiment with the commercialization of engineered crops resistant to the action of 2,4-D and Dicamba. These two herbicides will likely be used alone and in combination with glyphosate, despite a lack of knowledge about what usage pattern would be best for decreasing the emergence of resistance in weed populations while maintaining economic viability. This ignorance is reflected in the literature from the EPA and companies that simply tells farmers that diversified approaches to weed management are best for delaying resistance, but with no supporting evidence or incentives (*55*).

Governments and universities could adopt incentive systems to create landscape-level experiments to test different spray combinations, rotations, or combined cultural and chemical controls on large acreages. Genomic responses of weeds would be monitored carefully enough to eliminate any failed strategy before troublesome resistance evolved. Setting up such experiments would require large investments and highly skilled management of people and technologies. This may seem radical, but governments do make similar investments to decrease erosion, maintain conservation reserve programs, and subsidize crop-loss insurance. Lacking data from bold experiments, we will likely just learn that heavy use of 2,4-D and Dicamba results in weed resistance and that we have an even more critical need for herbicides with new modes of action.

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