

Transparency in risk-disproportionate regulation of modern crop-breeding techniques

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ABSTRACT

Despite over 25 years of safe deployment of genetically engineered crops, the number, complexity, and scope of regulatory studies required for global approvals continue to increase devoid of adequate scientific justification. Recently, there have been calls to further expand the scope of study and data requirements to improve public acceptance. However, increased regulation can actually generate consumer distrust due to the misperception that risks are high. We believe risk-disproportionate regulation as a means to advocate for acceptance of technology is counter-productive, even though some regulatory authorities believe it part of their mandate. To help avoid public distrust, the concept of regulatory transparency to demystify regulatory decision-making should be extended to clearly justifying specific regulatory requirements as: 1) risk-driven (i.e., proportionately addressing increased risk compared with traditional breeding), or 2) advocacy-driven (i.e., primarily addressing consumer concerns and acceptance). Such transparency in the motivation for requiring risk-disproportionate studies would: 1) lessen over-prescriptive regulation, 2) save public and private resources, 3) make beneficial products and technologies available to society sooner, 4) reduce needless animal sacrifice, 5) improve regulatory decision-making regarding safety, and 6) lessen public distrust that is generated by risk-disproportionate regulation.

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Public Acceptance

Prior to approval, global regulatory authorities assess the safety of genetically engineered crops in the context of human food, animal feed, and the environment. Several of these regulatory authorities have (or claim) a mandate to not only assess safety, but also to improve the public's confidence in regulatory decisions through risk communication.^{1–3} Despite over 25 years of successful deployment of genetically engineered crops, the number, complexity, and scope of regulatory studies required for global approvals continue to increase irrespective of the demonstrated benefits and safety observed during their widespread use globally.^{4,5} Recently, there have been calls to further expand the scope of studies that investigate consumer safety concerns in support of regulatory approval of products developed using genetic engineering.^{6,7} Inclusion of regulatory data requirements that do not materially inform the safety assessment continues to be promoted by some stakeholders, scientists, and technological specialists in the name of

public acceptance of these technologies, especially in regions that have historically been against deployment of these innovative advances.^{1,2,8}

Risk-disproportionate Regulation Increases Perception of Risk

However, public distrust often stems from ethical (e.g., corporate and government distrust) and ideological (e.g., “unnaturalness”) concerns, which are unlikely to be addressed through additional scientific data provided by developers.^{9,10} Furthermore, most public distrust of genetically engineered food does not seem to discriminate among specific products of genetic engineering but is instead directed toward the technology as a whole, as evidenced by labeling of consumer products, as simply “GMO” or “non-GMO”, with the latter being purely a marketing tool.¹¹ Contrary to the intention of improving public acceptance, risk-disproportionate regulation may

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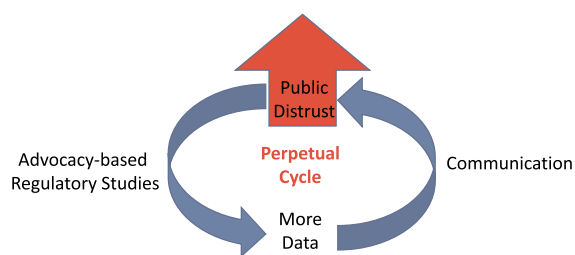


Figure 1. Vortex of increasing regulation fueling increased public distrust, prompting more regulation.

be leading to increased, rather than decreased, consumer distrust of modern breeding techniques, thus strengthening opposition in regions where these beneficial products are already distrusted at an emotional level.^{12–15} When this occurs, a cycle of increasing public distrust leading to increased regulatory requirements can perpetuate both public distrust and risk-disproportionate regulation (Fig. 1).

Transparency

To further gain public acceptance, increased transparency by regulators has been proposed as a means to demystify regulatory decision-making and increase public trust in regulatory decisions.¹⁶ Although we believe that risk-disproportionate regulation in the name of advocating for acceptance of genetically engineered crops is counterproductive, some regulatory authorities believe it is part of their mandate, sometimes even in the absence of legal authority to do so. In these situations, we advocate for extending the concept of regulatory transparency to not only demystify regulatory decision-making, but also to clearly stating the justification of specific regulatory requirements. We suggest that regulators who persist in requiring risk-disproportionate data, with the intent of addressing consumer distrust, explicitly categorize data and study requirements as: 1) risk-driven (i.e., proportionately addressing increased risk compared with traditional breeding), or 2) advocacy-driven (i.e., primarily addressing consumer concerns and acceptance both for the specific product and the underlying technology, but where the risk is no higher than for traditionally bred crops) (Fig. 2). Without this context, data transparency can only further increase, rather than decrease, public distrust.¹⁷

This demarcation of regulatory studies as risk-driven or advocacy-driven would help reduce the misperception by the public that extensive and complex regulatory requirements for products developed through modern breeding techniques are in place to address inherently higher safety risks. This suggestion derives from the assumption that studies intended to assess plausible safety concerns are more intrinsically important than studies intended to promote consumer acceptance of these technologies and products.^{3,5,13}

Prescriptive Regulations

All regulatory studies should be consistent with good science, but not all studies require a highly prescriptive and harmonized study design to be reliable and informative. Many studies that rigorously support a particular safety conclusion, but do not adhere to existing prescriptive regulatory requirements, would easily meet standards for peer-reviewed scientific publication. For studies that address a plausible safety concern, prescriptive studies are sometimes desired to maintain consistency in decision-making across regulatory submissions. However, it seems unreasonable and counterproductive to reject an applicant's scientifically rigorous study because of a trivial deviation from a highly prescriptive, templated, study design when that study is required primarily to improve consumer acceptance; as such, rejection neither improves the safety assessment nor the likelihood of consumer acceptance.³ However, without clearly separating those studies that are required for evaluating risk from those that are primarily designed to improve consumer acceptance, regulators have no clear criteria for judging which studies might benefit from adherence to highly prescriptive regulatory requirements and which should accommodate a more flexible study design. Therefore, clarification on the primary purpose for each specific regulatory requirement seems generally beneficial to study scientists, regulatory reviewers, and the public.

Example of Crop Composition Study

Biochemical composition studies for genetically engineered crops were originally required to assess potential unexpected adverse effects of the then-

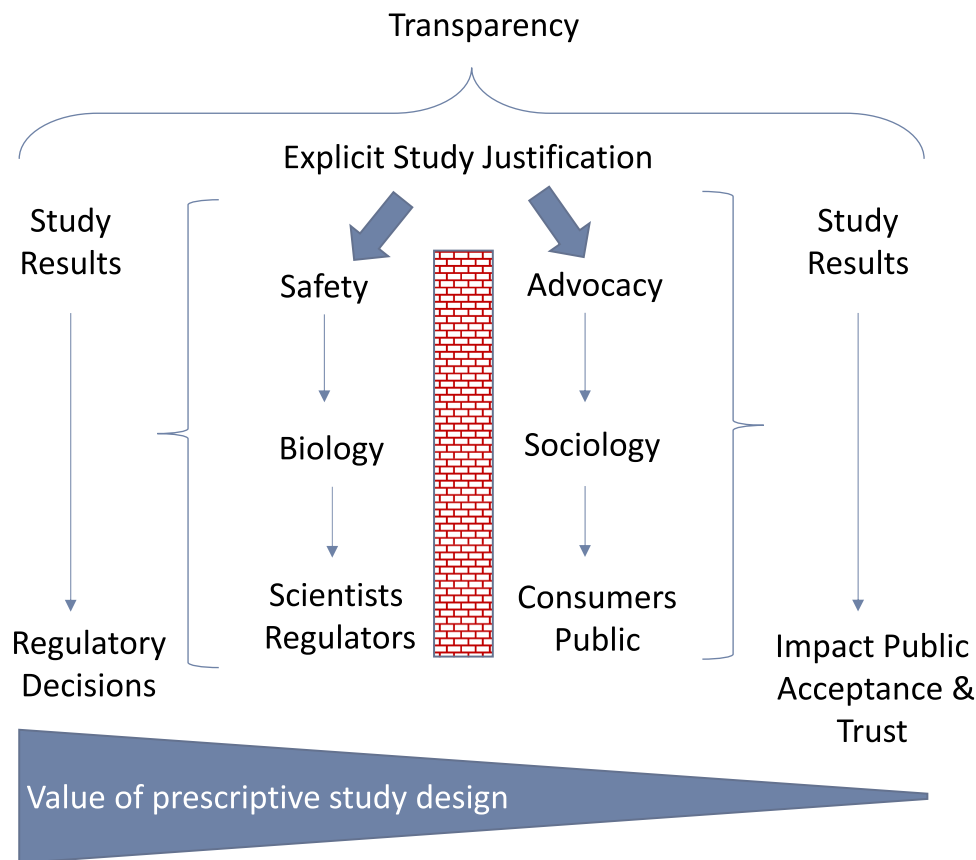


Figure 2. Schematic showing benefit of explicitly justifying studies as designed to 1) evaluate proportionate risk or 2) advocate for public acceptance where risk is no greater than for traditionally bred crops.

nascent transgenesis process. These studies have served well to validate the substantial equivalence between genetically engineered crops and their non-genetically-engineered counterparts. Indeed, a quarter of a century of research has now empirically demonstrated that transgenesis is very specific to the intended or desired effect and causes fewer and less-impactful unexpected effects on crop composition compared with traditional breeding.^{18–23} Furthermore, our improved understanding of the molecular underpinnings of genetic modification now mechanistically explains why modern breeding techniques cause fewer unexpected compositional effects compared with other common breeding methods.²⁴

Irrespective of this improvement to our scientific understanding, ever-increasing prescriptive and complex regulations have driven the cost of crop composition studies to over a million US dollars and have extended approval times due to the increased duration required to conduct each study and answer the numerous questions posed by

regulators.^{18,25,26} From a scientific perspective, the study design for crop composition evaluations should be based on plausible mechanisms by which the genetically engineered trait could impact biochemical pathways in the crop to cause a specified adverse effect that is likely to cause harm.^{12,21} In the absence of any reasonable hypothesis for an adverse effect, the current approach of measuring a catalog of compositional analytes in samples collected from replicated field plots grown at multiple locations is not scientifically justified and fails to inform the safety of genetically engineered crops. These concepts are equally applicable to the array of agronomic and phenotypic characteristics assessed in these same field trials.²⁷

However, the continued practice of hypothesis-free testing with a multitude of compositional analytes has been justified by some to improve consumer acceptance of genetically engineered crops, perhaps because the scientific rigor of safety assessment is mistakenly equated with the quantity of data the applicant must provide.²⁸ Ignoring the concept

of proportionality, calls to increase the complexity of regulatory studies using metabolomics, transcriptomics, and proteomics are being made with the stated motivation of further improving consumer acceptance of modern breeding techniques.^{7,29,30} Yet, there have been few calls to explicitly state this advocacy-based motivation in regulations. Furthermore, it seems doubtful that applying omics technology to composition studies would actually improve consumer acceptance due to the low awareness of omics technologies by the general public and the unlikely outcome that applying omics technology to composition studies would quell the underlying consumer distrust of corporations and governments and the perceived “unnaturalness” of modern breeding techniques.¹⁴ It is noteworthy that there are also technical difficulties in interpreting omics data in the context of safety assessment due to the absence of baseline data that delineate profiles that raise safety concerns.^{31,32} Consequently, requiring omics data will not only fail to improve public acceptance, but also is likely to worsen regulatory decision-making and increase risk.³³

As a result of not explicitly acknowledging that continually spiraling regulatory requirements for crop composition studies are only justifiable based on an effort to gain consumer acceptance, these studies largely evaluate a negligible safety risk using a study design that is likely unappreciated by the public. Thus, entangling safety studies with those primarily intended to improve consumer acceptance, at best, does not respect the public’s ability to understand the difference in the motivations for requiring these studies, and, at worst, is deceptive in implying that the technologies being assessed are a higher risk than alternative technologies that are largely unregulated, or that more data equals greater rigor.^{12,14,28}

Example of 90-day Rat Feeding Study

Even more unfortunate, the European Food Safety Authority (EFSA) has developed highly prescriptive regulations for a hypothesis-free, 90-day whole-food rat feeding study for genetically engineered crops, even though EFSA experts indicated that such studies are unnecessary unless a hazard is identified from other information.^{34,35} While the

European Commission requires such studies be conducted with new individual transgenic events, EFSA has recently begun requiring studies be repeated for individual transgenic events in breeding stacks even though they were previously completed under international guidance and prior EFSA requirements and there is no new risk hypothesis (<https://www.efsa.europa.eu/sites/default/files/event/181024-p7.pdf>). This retroactive requirement adds nothing to the safety assessment, requires the expenditure of resources by both regulators and applicants, delays regulatory decisions, and results in the unnecessary sacrifice of animals.

Designating the justification for such studies as promoting public acceptance may have avoided the development of such highly prescriptive regulations as well as the requirement to retroactively apply them to products that are already approved. In this example, even the regulatory authority clearly does not support this study as generally being required to determine safety.

Conclusions

Although risk-disproportionate regulation is likely to increase public distrust, some regulatory authorities continue to justify risk-disproportionate regulation as improving trust in products derived from modern biotechnology. In addition, the authorities advocate for transparency of the information submitted to support regulatory submissions and the decision-making process to further improve public acceptance. In the limited circumstance where legal frameworks provide the regulatory purview to consider customer preferences in addition to safety, we propose that transparency should extend to explicit communication of the advocacy purpose of studies that are conducted when the risk of modern breeding techniques is no greater than for crops developed using traditional breeding methods. Such transparency in the motivation for requiring risk-disproportionate studies would: 1) lessen over-prescriptive regulation, 2) save public and private resources, 3) make beneficial products and technologies available to society sooner, 4) reduce needless animal sacrifice, 5) improve regulatory decision-making regarding

safety, and 6) lessen public distrust that is generated by risk-disproportionate regulation.

Disclosure of potential conflicts of interest

RH, NS, JA, FA, and FC are employed by Corteva Agriscience which develops and markets transgenic seed. AR has no conflict of interest.

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