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Why reinvent risk?

To the editor:

I read with great interest the two commentaries in the November issue by Goklany (*Nat. Biotechnol.* **20**, 1075, 2002) and Auberson-Huang (*Nat. Biotechnol.* **20**, 1076–1078, 2002) regarding the risk assessment and the "precautionary principle" as applied to genetically modified organisms (GMOs). In my view, neither author makes a critical distinction between the scientific and analytical process of risk assessment and the policy stance of the precautionary principle, neither acknowledges the impact of uncertainty on decisions, and neither offers a useful framework to address fully the complex decisionmaking associated with GMOs.

In theory, the process of risk assessment and precautionary policy can be integrated into an analytical decision framework, which I believe is what both authors are attempting to define, but their definitions are incomplete. Risk assessment is a scientific process that estimates the probability and severity of adverse events[1]. This process is independent of stakeholder or risk manager viewpoints. Essentially, the precautionary principle is a policy guiding risk management that states that reduction or elimination of risk is an overriding decision objective (over and above that of trade-offs like cost, competing risks, etc.). If that policy is adopted, it does not replace or inform risk assessment; it simply provides a means to guide risk management based on the results of risk assessments.

Thus, Auberson-Huang appears to have it backwards. As typically applied, the precautionary principle hamstrings true stakeholder involvement and proper risk management by constraining elicitation of stakeholder values and the scientific process of risk assessment with predetermined conclusions and the refusal to acknowledge trade-offs. Goklany argues that we should assess one set of these trade-offs through risk–risk analysis so as to be "precautionary," but this is an inferior substitute for a true decision framework using a decision criterion such as net benefit. Risk–risk analysis does not directly address stakeholder values, nor the complete range of trade-offs associated with adoption of a particular policy. Neither author explicitly addresses the central problem that the risks, benefits, and costs associated with many GMOs are highly uncertain, and that rigorous, quantitative assessment of the impact that uncertainty has on decisions is critical to informing stakeholders and decision makers, as well as informing primary research.

A proper decision process will integrate the science of risk assessment with the policy of risk management, but to my knowledge this is not occurring with GMO issues. It is unfortunate that many of the same mistakes that have been made historically in the environmental toxicology field and other fields are now being made with regard to GMOs. The appropriate and acknowledged way to evaluate these highly uncertain risks is to employ risk assessment as a scientific process within a decision framework that directly addresses stakeholder values and the impact of uncertainty on decisions. There is a wealth of literature and applications regarding such frameworks, such as multiattribute utility theory and multicriteria decisionmaking, that do exactly this[2]. It is time to acknowledge that policy approaches, such as the precautionary principle, and halfway measures such as risk–risk analysis, are insufficient to address the complex decisionmaking that is associated with GMOs.

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1. Haimes, Y.Y. *Risk Modeling, Assessment, and Management* (Wiley, NY, 1998).
2. Cox, L.A. *Risk Analysis: Foundations, Models, and Methods* (Kluwer Academic Publishers, Dordrecht, 2001).

Telomere-driven replicative senescence is a stress response

To the editor:

In the July issue, Rubin (*Nat. Biotechnol.* **20**, 675–681, 2002) and Wright and Shay (*Nat. Biotechnol.* **20**, 682–688, 2002) presented two contrasting views of the nature of *in vitro* replicative senescence and its importance for ageing *in vivo*. Rubin emphasized the marked stochastic variation in doubling potential of individual cells and its apparent inconsistency with the idea that telomere reduction acts as a mitotic clock (as a result of the end-replication problem—i.e., the inability of conventional polymerases to replicate fully the very end of a linear DNA molecule). Wright and Shay argued that the stochastic loss of growth potential results from a "stimulation and stress-induced senescent-like arrest," or stasis, which is not "true" senescence. In this exchange, stasis and senescence were presented as a pair of complementary, but essentially different processes, stasis being telomere-independent and, most often, stress-induced, senescence being induced by telomere dysfunction and stress-independent. We believe this dichotomy is misleading and overlooks the growing evidence that telomere shortening is stress-dependent.

Although stress can induce telomere-independent growth arrest, and telomeres can shorten as a result of the end-replication problem in the absence of stress, stress is one of the major influences on the rate of telomere loss. Chronic mild oxidative stress accelerates telomere shortening and shortens replicative lifespan, whereas free-radical scavengers[1] or overexpression of the antioxidant enzyme superoxide dismutase[2] do the reverse.

Under constant levels of extrinsic oxidative stress, there is a substantial inverse correlation between antioxidant capacity and telomere-shortening rate in human fibroblast strains[3]. Telomeres are more sensitive to oxidative damage[4], and single-strand breaks in telomeres are less well repaired than elsewhere in the genome. This leads to an accumulation of telomeric damage, which is quantitatively transformed into faster telomere shortening during DNA replication[1]. Together, these data show that on top of the end-replication problem, oxidative stress is a major cause of telomere shortening. Moreover, they indicate that the shortening of replicative lifespan induced by mild oxidative stress is mediated by its effect on telomeres.

If oxidative stress is indeed playing a major role in telomere loss, the heterogeneity in cell-doubling potential of cultures like WI-38 and MRC-5 fibroblasts should be linked to a corresponding stress-dependent heterogeneity in telomere-shortening rates[1]. To test this suggestion, we employed fluorescence-activated cell sorting (FACS) to select a subpopulation of midpassage MRC-5 (PDL 31) fibroblasts exhibiting the senescence phenotype, as characterized by large size (forward scatter) and high lipofuscin content (autofluorescence in FL1; ref. 5).

Re-analysis of the sorted cells indicated an at least 3-fold enrichment of phenotypically senescent cells. Few of the sorted cells had undergone DNA synthesis (according