tide. Our results broaden the hypothesis of Mourez *et al.* that the YWWL sequence may bind to the PA heptamer at the hydrophobic area that interacts with the EF/LF factors (Fig. 1B,C), and identify the crucial site.

Using the technology devised for a much-publicized distributed-computing screensaver project[4], which now uses more than 1 million computers, we plan to initiate a massively distributed search among a virtual library of 3.5 billion small molecules for compounds that can bind to the PA heptamer–binding site identified by our algorithm[2]. Our approach may suggest new molecules that can prevent the assembly of the anthrax toxin complex.

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## Rethinking substantial equivalence

*To the editor:*

In 1993, the Organisation for Economic Cooperation and Development (OECD; Paris) introduced the concept of substantial equivalence as a guiding principle for safety assessment of food containing a GM component. Since then, several meetings of experts sponsored by the OECD or jointly by the Food and Agricultural Organization (Rome) and World Health Organization (Geneva, Switzerland) have endorsed the use of this concept in regulatory decision-making. Under European Union (EU; Brussels) "Novel Food" Regulation 258/97, establishment of the "substantial equivalence" of a GM food (component) also is used to determine whether a "light" notification procedure or a "heavy" authorization procedure is followed for a particular product.

In recent years, scientists concerned about the potential health risks of GM foods have challenged substantial equivalence as inadequate for assessing food safety. In 1999, for example, a commentary in *Nature*[1] labeled the concept "inherently anti-scientific because it was created to provide an excuse for not requiring biochemical and toxicological tests."

Against this background, our consultancy was commissioned by the Dutch Consumentbond and the European consumer organization Bureau Européen des Unions de Consommateurs (BEUC) to study the application of substantial equivalence in the EU, so as to provide input to a workshop organized by BEUC in September 2001[2].

To that end, we analyzed several notification dossiers for products derived from GM varieties of maize and refined oil derived from GM varieties of oilseed rape. Our analysis showed that compositional data submitted on the content of macro- and micronutrients, vitamins, inherent plant toxins, and anti-nutrients lacked consistency from case to case. Furthermore, the design of the GM crop field trial, the geographical locations and seasons of planting and harvesting, and the choice of control differed considerably from case to case. These case studies illustrated the lack of an operational definition of the concept of substantial equivalence in the EU.

As an alternative model, we have proposed that an operational definition for food-safety assessment should include a minimum list of macro- and micronutrients, anti-nutrients, inherent plant toxins, secondary metabolites, and allergens to be analyzed for each GM crop species and of their baseline concentrations in conventional varieties. It is also necessary to create detailed protocols to guide the design of field trials, to establish validated techniques that can reliably ascertain the content of these compounds in plants, and to use common methods to analyze the data statistically.

The participants at the BEUC workshop concluded that "substantial equivalence" has been a controversial and misleading term for consumers that should not be used in regulatory decision-making. They recognized that it remains crucial to systematically detect unintended changes in the composition of GM crops compared with an appropriate control, as such changes may be of toxicological, immunological, or nutritional concern.

The OECD, the European Commission, EU member states, and the European biotechnology industry association (EuropaBio) are now drafting "minimum lists" to underpin "substantial equivalence." Although this is a good first step, there are some discrepancies among these drafts. For example, in the case of GM maize, the Dutch authorities have required additional data about five secondary metabolites that have not been included in the list proposed by EuropaBio. Despite these differences, the efforts made by different bodies to standardize these lists should be welcomed.

In July 2001, the European Commission proposed to abandon the "light" notification procedure, which would mean that all GM food (components) would need to undergo a full authorization process. Their safety assessment obviously still requires a systematic detection of unintended changes GM food (components) compared with an appropriate control. But whether it is useful in that context to cling the term "substantial equivalence" is doubtful.

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## ES cell media

*To the editor:*

The article by Xu *et al.* in the October issue describes the successful feeder-free propagation of undifferentiated human embryonic stem (ES) cells (*Nat. Biotechnol.* **19**, 971–974, 2001). The authors reported, however, that in conditioned media from mouse embryonic cell lines and from human immortalized lines, the feeder-free human ES cells did not retain all the features of cells grown on feeder layers.

Did Xu *et al.* have the occasion to test human embryonic fibroblasts, which are available from cell repositories like the American Type Culture Collection (Manassas, VA) and the European Collection of Cell Cultures (Salisbury, UK), as feeders or as a source of conditioned medium? The answer might be of great help to the growing scientific community involved in the study of human ES cells.

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*Chunhui Xu and Melissa Carpenter reply:*

We demonstrated that human embryonic stem (hES) cells can be maintained on appropriate matrices and media conditioned by irradiated primary mouse feeders (MEF-CM) while maintaining all of the essential features of hES cells grown on feeders. When hES cells were grown in conditioned media from a human telomerase immortalized neonatal fibroblast line (BJ5ta) and embryonic murine fibroblast lines (NHG 190 and STO), fewer colonies with appropriate morphology were observed. Evaluation of additional immortalized human cell lines is currently in progress.

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