demonstrate the opposite—a significant reduction of nontarget invertebrates in Cry1Ab maize generally, and for MON810 maize specifically, when the comparators were fields with no insecticide applications. This was based on analyses of 24 studies and 415 tests in the former, and 11 studies and 235 tests in the latter. When non-GM fields were sprayed with insecticides, there was a higher invertebrate abundance in Cry1Ab maize generally, but not in MON810 (based on 8 studies/90 tests and 4 studies/39 tests, respectively). This means that for GM crops generally and for the European controversy surrounding the approval of MON810 specifically, depending on what is considered to be the appropriate comparator for defining adverse effects, the body of available scientific knowledge leads to alternative conclusions. Romeis *et al.*[1] have inserted a (legitimately debatable) policy norm into their 'science' and then tried to suggest that their conclusions are final.

What is a relevant comparator, and other questions raised by Romeis *et al.*[1], including what are our environmental protection goals and therefore what do we deem relevant risk-based science for policy, are not scientific questions alone but rather questions for policy authorities accountable to democratic processes. These types of questions are part of what has been termed 'risk assessment policy' (RAP)[8]. RAP is a normative process that both precedes and iterates with scientific risk assessment, shaping its orientation, boundaries, mandate and inferences, which makes risk assessment not exclusively a scientific process, as claimed by Kuntz *et al.*[9] in another recent Correspondence in *Nature Biotechnology*. The significance of this has been recognized by organizations, such as the United Nations Food and Agriculture Organization (Rome), the World Health Organization (Geneva), the US National Research Council (Washington, DC) and the European Commission (Brussels)[10]. The question of how to judge the relevance of a scientific study for risk assessment should therefore not be restricted to the scientific community (or worse to a small set of self-appointed researchers), but rather is an issue that requires broader-based and accountable consideration.

In addition to the question of relevance, the question of quality in science for policy also requires broader-based consideration. This is because what we are dealing with here is not simply a romanticized pure science with no social context or consequences, but rather a science specifically conducted to inform policy-making in a controversial arena of great public interest (i.e., the future of food production and biodiversity). Given this, the task of defining the criteria for evaluating quality cannot be legitimately nor sufficiently decided by Romeis *et al.*[1] alone, nor even the world of their peers. It is not for an esoteric group of researchers or experts to pronounce what constitutes quality in science for policy and then dismiss as irrelevant and unreliable any other science not corresponding with how their own particular interests and values have defined what is important. This issue also deserves (and in a democratic society, demands) deliberation across a wide range of stakeholders and implicated actors.

Such broad-based deliberation on quality criteria is crucial, not because science "is simply a matter of opinion, no better than any other opinion,"[9] but because, as Romeis *et al.*[1] correctly highlight, scientific research can be conducted under a range of test protocols and study designs, with the potential for each of these to lead to contrasting results. Which of the range of possible research approaches is best, with the most relevance for risk assessment and the highest quality as fit for purpose, will inherently depend on what questions are deemed most salient and what is most valued by a broad section of society. That is, it is both a scientific and a social matter.

What is at stake here is not only the future of GM crops but also the role and scope of scientific inputs to governance processes; thus, it is crucial that we maintain and enhance the credibility and legitimacy of those inputs. This requires, *inter alia*, impartial and consistent quality evaluation of all scientific studies, no matter what their conclusions.

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Romeis *et al.* reply:

We believe that Wickson *et al.*[1] have confused different elements of an environmental risk assessment (ERA), and did not understand or chose to ignore the purpose of our original Correspondence[2]. In addition, we strongly disagree with their contention that we believe that a "careful evaluation is only necessary or important" for "studies with findings challenging the dominant wisdom" when our Correspondence clearly describes the importance of ensuring the quality of all data that are used to inform environmental risk assessments.

Various stakeholders, including society writ large, should be involved in defining which elements of the environment are valued and should be protected from harm (i.e., protection goals). Even so, in the context of risk assessment and regulation of transgenic plants, it is the responsibility of both the scientists conducting the work and the regulators who interpret their results and conclusions to ensure that experimental studies are conducted properly. A concern about transgenic maize events that produce the Cry1Ab protein from *Bacillus thuringiensis* (*Bt*) is their potential to harm arthropods outside the order of the target pests, that is, Lepidoptera. This concern is derived from the value that society places on many of these nontarget arthropods (NTAs) because of the important ecosystem services they provide, such as biological pest control, pollination and decomposition. For insecticidal *Bt* maize to cause harm to a nontarget species, the species must be sensitive to the insecticidal protein; the associated risk hypothesis is "The *Bt* protein is not toxic to valued nontarget species at concentrations present in the field."[3] To test this hypothesis, purified Cry1Ab protein or *Bt* maize tissue that contains Cry1Ab is provided to nontarget species in controlled laboratory studies. As we state in our Correspondence, such NTA studies need to be carefully designed to obtain high confidence in the results and to minimize the possibility for false positives and false negatives.

Together with a group of scientists that have experience in the design of such toxicological studies (both from academia and the private sector) or expertise in the critical evaluation of such studies (regulatory authorities), we have previously provided a description of design criteria that should be followed to enhance the quality, reconstructability and reliability of NTA studies[4]. These criteria apply equally to all such studies, irrespective of who conducts them or how they may be used or communicated (e.g., in a scientific journal or as part of a regulatory dossier). For our Correspondence, we analyzed available peer-reviewed publications where the impact of Cry1Ab on nontarget organisms was tested and found that studies that reported adverse effects of Cry1Ab on non-Lepidoptera species shared one or more design elements that confound definitive conclusions about the toxicity of Cry1Ab, and hence are of limited value for ERA and subsequent regulatory decision making (see Supplementary Notes and Table 1 from our Correspondence). We chose the example of Cry1Ab for two reasons: first, there is an abundance of published literature available on the nontarget effects of Cry1Ab and *Bt* maize; and second, the interpretation of the results of a subset of these studies has been used to justify a ban on the cultivation of *Bt* maize event MON810 in countries such as Germany and France, where such outlier studies have been selectively cited as new evidence of harm to the environment.

We reject the statement that not all publications were analyzed with the same level of scrutiny. The main study quality criteria are plotted for all published nontarget studies with purified Cry1Ab or Cry1Ab-expressing maize tissue in Supplementary Table 1. Out of these studies, four were highlighted in the main body of the text because they have received considerable attention in the press and have been used as an argument to justify regulatory bans of *Bt* maize MON810. Thus, they are best suited to illustrate the impact of individual studies on regulatory decision making, which was the primary focus of our Correspondence.

As correctly stated by Wickson *et al.*[1], Supplementary Table 1 in our original Correspondence lists a few other studies that reported adverse effects. These studies, however, received little or no attention in the press and appear not to have influenced any ERAs, but we are pleased to address them here. In these studies, the authors themselves could not confirm the results in parallel experiments described in the same publication that were conducted using a test substance containing higher concentrations of Cry1Ab (study nos. 7, 18, 27 and 46) or using plant tissue from other varieties of MON810 (study nos. 50 and 51). This information is provided in the footnotes of the original table. One of the studies (no. 9) is inconclusive because no appropriate negative control was included.

On another point, we reject the statement by Wickson *et al.*[1] that we only regard studies showing negative effects of the *Bt* toxin Cry1Ab on nontarget organisms as "nonconclusive." Such a judgment applies to some studies in which there was no observed adverse effect of a *Bt* treatment. This includes studies that used *Bt* maize pollen from events MON810 and Bt11, which are known to contain very low levels of Cry1Ab (in the nanogram per gram pollen range). These examples are described in the Supplementary Notes and Table 1 of our original Correspondence. These studies, however, do not challenge the outcome of the risk assessment that was conducted before the cultivation of Cry1Ab-expressing *Bt* maize.

We are pleased that the respondents agree that test substance purity, homogeneity and equivalence between the purified and plant-expressed Cry1Ab are important criteria to consider when designing and evaluating nontarget studies using purified Cry1Ab (but not when using *Bt* maize tissue as test substance). These are essential criteria that are evaluated for regulatory toxicity studies but generally are given little attention in the peer-reviewed literature (again this was addressed in the Supplementary Notes and Table 1 of the original Correspondence). In our experience, purity of the Cry1Ab protein and uniform distribution in the artificial diet are readily achieved, whereas testing for equivalence to the plant-produced protein is typically not addressed in the peer-reviewed literature.

Poorly designed or executed studies pose a serious problem when methodological errors are missed or ignored. As we state in our Correspondence, this applies to studies that report false positives or false negatives. Contrary to the respondents' suggestion, our contention is not that outlier studies should be dismissed but that they should be carefully evaluated, particularly when they are used to over-ride the conclusions of prior risk assessments. For example, MON810 was approved for cultivation in the European Union based on the risk assessments conducted by the GMO Panel of the European Food Safety Authority (Parma, Italy), which concluded that MON810 is unlikely to have any adverse effect on the environment in the context of its intended uses[5–7]. To date, there is no verified evidence that the Cry1Ab protein produced by *Bt* maize affects NTAs outside the order of Lepidoptera. According to Wickson *et al.*[1], this no-risk conclusion is challenged by a meta-analysis of NTA data collected in various field studies of Cry1Ab maize. Indeed, the meta-analysis by Marvier *et al.*[8] reported that "the abundance of non-target invertebrates was significantly lower in *Bt* compared with that in control fields that lacked insecticide applications." The authors, however, also make clear that this difference was caused by a significant decline in Hymenoptera in *Bt* maize. Subsequent analyses of the same and expanded data sets showed that the decline in Hymenoptera was exclusively due to the decline in a specialist parasitoid of the European corn borer, the target pest of the *Bt* maize[9,10].

The decision to approve a transgenic plant should be informed by scientific and social considerations, which is why the identification of protection goals derived from legal instruments or environmental policies (which should be established in response to societal priorities) is so essential to problem formulation for ERA. We agree with Wickson *et al.*[1] when they write, "it is not for an esoteric group of researchers or experts to pronounce what constitutes quality in science for policy and then dismiss as irrelevant and unreliable any other science not corresponding with how their own particular interests and values have defined what is important." This is exactly why we have emphasized the importance of evaluating NTA studies against criteria that consider the key elements of experimental design that are needed to ensure that conclusions are supported by accrued and accurate data. This should be an objective exercise that is exclusively science-based; the conduct and evaluation of studies designed to measure the potential adverse impacts of a Cry protein, such as Cry1Ab, on NTAs are undertaken to address a plausible risk hypothesis. This is not "science for policy" but science to inform a product-specific environmental risk assessment. This distinction is critical.

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Rational drug repositioning by medical genetics

To the Editor:

Drug repositioning has been regarded as one of the most promising strategies for translational medicine. Common efforts to find new uses for existing drugs depend on text mining[1], chemical genetics[2] and network analysis[3]. In the April 2012 issue, Sanseau *et al.* proposed the use of genome-wide association studies (GWAS) for drug repositioning[4]. This strategy is consistent with the concept that human disease genes are highly druggable and that indications of derived drugs frequently match genetic disease traits[5,6]. Genetic diseases may result from loss of function (LOF) or gain of function (GOF) of mutated genes, and ligands may behave as agonists or antagonists of targets[6]. If a disease corresponds to a genetic disorder that arises from the GOF (or LOF) of mutated genes, antagonists (or agonists) for the target genes will be potential drugs[6], whereas agonists (or antagonists) will exert undesirable effects. Therefore, medical genetics–based drug repositioning can be enhanced with information regarding the pathogenesis of genetic diseases and the action mode of ligands.

The catalog of published GWAS data from the US National Human Genome Research Institute does not provide detailed pathophysiological information on genetic diseases; thus, the new uses of old drugs predicted by the GWAS may be side effects. For instance, it was suggested that basiliximab (Simulect) and daclizumab (Zenapax), which target interleukin-2 receptor alpha (IL2RA), might be applied for the treatment of type 1 diabetes[4]. However, as recorded in Drugs.com, diabetes is the clinically identified side effect of the two drugs. The underlying reason is that LOF variation in IL2RA results in type 1 diabetes[7], and both basiliximab and daclizumab are IL2RA antagonists. Thus, it can be inferred that agonists for IL2RA could be appropriate for the treatment of type 1 diabetes, a hypothesis that is preliminarily supported by the experimental observation that the IL2RA agonist aldesleukin (Proleukin; interleukin 2) has clinical anti-diabetic activity (http://clinicaltrials.gov/). Therefore, by analyzing information regarding the pathogenesis of genetic diseases and drug actions, we can provide more rational insights into drug repositioning and even predict drug side effects. This concept is validated by using medical genetics data from Online Mendelian Inheritance in Man (OMIM), which provides detailed pathogenic information on human disease genes.

We collected 269 successful human drug targets, which are modulated by 983 unique approved drugs, by retrieving the Therapeutic Target Database (TTD; **Fig. 1**). By comparing successful drug targets with 2,797 human disease genes recorded in OMIM (as of May 24th, 2012), we found that 131 (48.7%) successful targets were associated with inherited diseases (**Fig. 1**). The indications of drugs that target these genes were then manually compared with genetic disease traits. A total of 135 matches and 535 mismatches between drug indications and genetic disease traits were identified (**Supplementary Tables 1** and **2**). Examination of the matching drugs and disease traits revealed that all of the drugs are antagonists (or agonists) for targets with GOF (or LOF) features. The 135 matches notably included the most illustrative examples of identical matches derived from GWAS, such as that 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) can lower blood cholesterol levels (hypercholesterolemia)[4]. These matches validate the rationality principle mentioned above and strongly suggest that we can apply the principle to find new uses for old drugs and predict drug side effects based on mismatch information. For instance, drospirenone, a mineralocorticoid receptor (NR3C2) antagonist, has been approved as an oral contraceptive, whereas NR3C2 agonist fludrocortisone (Florinef) has been indicated for cerebral salt-wasting syndrome. Considering that the GOF alleles of NR3C2 are associated with hypertension, we infer that NR3C2 antagonists have anti-hypertensive effects, whereas NR3C2 agonists have hypertension-inducing side effects. Indeed, the anti-hypertensive potential of drospirenone and the hypertension-inducing property of fludrocortisone with salt have been observed experimentally (**Table 1**)[8,9]. The preliminary success of this methodology encouraged us to predict new indications and side effects for more drugs. Some illustrative examples that have been experimentally validated are listed in **Table 1**.

Etanercept is an inhibitor of tumor necrosis factor (TNF). Considering that the GOF alleles of TNF are associated with asthma, TNF inhibition is inferred to have therapeutic effects on asthma. Indeed, the anti-asthma activity of etanercept (Enbrel) has been observed in experiments[10]. Likewise, perindopril (Aceon), an angiotensin-converting enzyme (ACE) inhibitor, can be repositioned to treat Alzheimer's disease, because the disease may be caused by GOF mutations within ACE. This new indication of perindopril has been revealed in animal models[11].

Testosterone is a steroid hormone that functions as an agonist that targets the androgen receptor for male hypogonadism. The associated genetic diseases caused by GOF variants of androgen receptor involve prostate cancer. Thus, we infer that testosterone, as an androgen receptor agonist, cannot be repositioned for prostate cancer treatment but has prostate cancer–inducing side effects. Indeed, prostate cancer has been reported as a contraindication of testosterone replacement in men[12].