GM soybeans—revisiting a controversial format

To the editor:

I was grateful to you for inviting me to discuss some of my experimental results in *Nature Biotechnology*; however, the Feature entitled "[Genetically modified] GM soybeans and health safety—a controversy reexamined," as published in the September issue[1], presents a flawed picture of my work. Although I thank Bruce Chassy, Val Giddings, Vivian Moses and Alan McHughen (Chassy *et al.*) for their detailed analysis of my work, remarks and recommendations, I am concerned that your readers will be misled by several of their comments. I also would like to clarify some issues concerning the manner in which this article was commissioned, a process that raises questions about editorial standards and practice at your journal. In my comments below, I first address the questions raised about my experiments and findings in the order in which they were raised in the Feature. I then raise some general concerns about the commissioning, proofing and production process. And, finally, I outline my responses to the criticism in the Feature of my research.

On p. 981, Chassy *et al.* remark that it is "not possible" for me to have obtained Roundup Ready (RR) line 40.3.2 soybeans from the Netherlands supplier of Archer Daniels Midland (ADM; Decatur, IL, USA), adding "the best that can be said is that commercial products sold by ADM would have been an indeterminate and variable mixture of conventional and non-GM soybeans." On the next page, they assert that I "provided no PCR evidence that the Arcon SJ product did not contain the CP4 5 EPSPS [enolpyruvyl shikimate-3-phosphate synthase] gene or the CP4 EPSPS protein it encodes. These assays are necessary to demonstrate that this control is in fact a non-GM-containing material." I can only state that my laboratory did receive soy clearly labeled as GM and non-GM soy. Quantitative analysis of RR soy using the 'CP4-LEC-RT-PCR' construct confirmed the presence of this transgene in 100% of the GM soy flour. In the traditional, non-GM soy flour, only traces (0.08 ± 0.04%) of the same construct were present. In fact, we checked all kinds of soy. The analysis of GM soy and non-GM soy was performed by 'blinded' operators (see **Fig. 1**).

Chassy *et al.* also note, "Ermakova states that males were not exposed to soy; however, they were placed into cages with females to which soy was provided every day. Consumption of soy by males would have also reduced the ration of soy available to the females." The last supposition is incorrect. Although males did receive soy during mating—potentially competing for soy rations with females—during this period, the experimental diets of the females were also supplemented with extra soy to correct for any consumption by males. We also performed further investigations where both females and males received soy before and during mating. They state, "after 3 days, the males were moved to the cage of another female where they remained for three additional days." Again this is incorrect. Males were moved to their own cages after 3 days of mating; they were not moved to the cage of another female because we were going to use pups from different parents to obtain the next generation.

Later on the same page, Chassy *et al.* write, "Ermakova states that in five trials a total of 100 animals have been studied, which translates to an average of 20 animals per study and ~5 for each experimental group." Chassy *et al.* also go on to criticize my study for having too few animals and cite as correct a study by Brake and Evenson[2]. I was very surprised by these remarks, because they are wrong. We studied 100 adult animals and 396 pups. To obtain the first generation in the main series of experiments, we used 9 females and 6 males (3 females crossed with 2 males in turn) in the control, GM-soy-fed and traditional-soy-fed groups. To clarify matters, I would like to add **Table 1**, which is similar, but not the same as Table 2 originally supplied by me and printed in the September Feature. In some cases, females didn't give birth; however, the reason for this can be clarified only after investigation of many more females and males. In addition a large number of pups (up to 89) were studied in each of these groups (**Table 1**). To obtain the second generation, we mated 12 females and 12 males (3 females crossed with 3 males in turn). The research of Brake and Evenson differs from my work in that they used fewer animals for breeding and investigation in their feeding study. In addition, for each diet (transgenic or conventional soybean) in their multigenerational mouse study, they used the following breeding scheme: two females

Table 1 Comparison of different kinds of chow on rat pup mortality[a]

Groups	Number of females that gave birth from total used	Number of pups born	Number of dead pups	Dead pups/total born (%)
Usual chow	7 out of 9	74	6	8.1%
Chow with 14% GM soy content	7 out of 9	72	24	33.3%
Usual chow plus GM soy ~	6 out of 9	64	33	51.6%
Chow with 14% GM soy content plus GM soy	9 out of 9	89	46	51.7%

[a]By end of the third week of lactation.

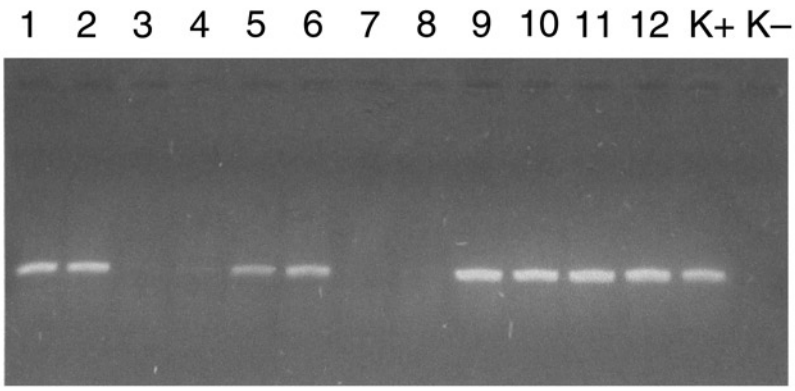

Figure 1 The 'blind' analysis of GM-soy and non-GM-soy samples using PCR. Lanes 1 and 2, GM-soy (flour); lanes 3 and 4, traditional soy flour; lanes 5 and 6, GM soy protein flour; lanes 7 and 8, traditional soy seeds; lanes 9 and 10, GM soy seeds after temperature treatment (t_o); lanes 11 and 12, GM soy seeds; K^+, positive control; K^-, negative control.

and two males were used to obtain the first generation; six females and three males were then used for each subsequent generation. Also Brake and Evenson studied many fewer pups in each group than we did in our experiments.

In discussing the number of animals studied and the pooling of results, Chassy *et al.* are also concerned that "... it is not standard practice to pool data from" different studies. Again, I disagree. In human studies, it is now, in fact, regarded as good practice to pool randomized, controlled, clinical studies across trials to get a better picture of the effect of the treatment on health and disease. My design merely substitutes rats for humans.

At the bottom of p. 982, Chassy *et al.* remark that "it is also not stated whether the litters were balanced with regard to number of pups and gender." The birth rate was similar in all groups: on average 10–11 pups per female (no significant difference). There were also no significant differences in body weights of males and females in all groups 2 weeks after birth. The data are as follows in the two series: in the control group (males, 30.2 ± 1.6; females, 30.7 ± 1.2); in the group receiving traditional soy (males, 27.0 ± 0.9; females, 26.3 ± 1.3); in the group receiving GM soy (males, 26.8 ± 2.0; females, 25.8 ± 1.6); and in the group receiving protein isolate GM soy (males, 27.1 ± 0.8; females, 26.3 ± 1.0). Similar data were obtained in other experiments.

When discussing my experimental design for the study, Chassy *et al.* comment that the 2-week timing for weight measurement of the animals makes "comparison with literature values difficult." Specifically, they say, "Parental animals should be weighed on the first day of dosing and each week after. Parental females should be weighed at a minimum on gestation days 0, 7, 14 and 21 and during lactation on the same days as the weighing of the pups. Pups should be weighed individually at birth, or soon thereafter, and on days 4, 7, 14 and 21 of lactation. Ermakova reports the weight of pups at 2 weeks of age." To clarify matters, the experimental design was as follows: we weighed males and females before mating, and then weighed males every week. We didn't weigh pregnant females because they had different numbers of embryos, which would have influenced their weights. We didn't want to touch pups and disturb their mothers and therefore didn't weigh pups during the first 2 weeks; females could have discarded pups if they were handled. Therefore, all pups were weighed 2 weeks after birth and most of them again 1 and 2 months after the birth.

My response to the remark that "no information is provided about external variables that can affect behavior, such as sound level, temperature, humidity, lighting, odors, time of day and environmental distractions" is that I could have provided this information if I had been asked: the cages of GM-fed and non-GM-fed animals were kept in the same room, so variables such as sound level, temperature, humidity, lighting, odors, time of day and environmental distractions would have been exactly the same between cages. Thus, the differences in health between the GM-fed and non-GM-fed groups observed in my study could not be attributable to external variables.

On p. 983, Chassy *et al.* comment "no actual data from behavioral studies are presented." The main focus of my research was to study the physiological state of rats, and then the effect of GM soy on their behavior. I believe that high mortality of pups, the small weights of some surviving pups and the absence of a second generation were the most important and disturbing results of my work. I feel that the data of my behavioral experiments, which I describe briefly below, could be the subject of a separate paper. There were very slight differences between groups in the open field (a standardized environmental arrangement for studying emotionality, spontaneous exploratory activity and locomotor activity). Even so, anxiety in the 'light-dark' test was higher in females, males and offspring receiving GM soy than in rats from other groups. Observed differences in behavior between the sexes of adult animals and also pups were found in this test. Males from groups fed GM soy had low horizontal and vertical activity, a small number of transitions and spent more time in the dark box than males from other groups. The same was true for the male pups. In contrast, females from groups fed GM soy and female pups from GM-soy groups were more active and restless, spent more time at the lit box and had more transitions than females from other groups. It was quite interesting that the pups displayed the same gender-related behavioral differences as adult animals. It is possible that the sex effect could be connected with the higher level of phytoestrogens in GM soy than conventional soy, according to the literature[3,4]. This suggestion is being verified by another research group. Preliminary studies in my laboratory to investigate the learning and memory of pups using a modified 'three-panel runway apparatus' indicate an impairment of learning in some tasks of pups from groups fed GM soy.

In discussing my results, Chassy *et al.* state "Previous reports in the literature have shown no effects of [Roundup Ready] RR soy on birth weights or pup mortality; they have also not shown any effects of RR soy on the testis or in the livers of male rats fed RR soy"[2,5,6]. Later, they concluded that the likely "explanation for the observed health effects [of GM soy] is poor experimental design and conduct as demonstrated by the exceptionally high mortality observed in the controls." It is necessary to emphasize that studies by these previous investigators had a different aim from my studies and thus they are not comparable. The mortality of pups depends on the feeding protocol and these previous investigators used a different protocol. Chassy

et al. also neglect to mention studies that have shown adverse effects of RR soy on testes and livers[7–9].

One of the common criticisms of toxicology studies attempting to assess the influence of GM products on animals is that investigations are performed under unnatural, laboratory conditions. My team tried to avoid this mistake by keeping as close to natural conditions as we could. It is known that in nature the pups have a mortality rate of ~10%. The mortality in our investigations was 8% in the control group (6 pups died out of 72 pups) and 10% in the group fed traditional soy, which is normal for animals in nature. As to their comment that I neglected to report pup mortality at days 0, 1 and 21 and failed to note "the timing and causes of death," I refer Chassy *et al.* to my published paper[10], which provides the times of pup deaths. We don't yet know the causes of pup death. To accomplish that it will be necessary to perform further biochemical, morphological and genetic studies.

In relation to my mating results, Chassy *et al.* draw the readers' attention to the Brake and Evanson[2] study, which "found no reproductive effects in mice in a multigenerational feeding study with RR soy." But this is an invalid comparison. In the experiments of Brake and Evenson[2] "pregnant mice were fed a transgenic soybean or a non-transgenic (conventional) diet through gestation and lactation.... Multigenerational studies were conducted in the same manner." Thus, the feeding regime for GM soy was completely different from the one used in my experiments, in which rats were offered a GM-soy diet 2 weeks before mating. In the Brake and Evenson experiments, EPSPS gene sequences could influence only embryonic cells in the womb; they could not affect sexual cells and/or organs before and during mating. In contrast, in my experiments, EPSPS gene sequences in GM soy would have had the chance to affect reproductive structures. Thus, my interpretation of these results is that the EPSPS gene sequences ingested by these animals can penetrate and affect rat sexual cells and/or organs[11].

I would also like to point out that Chassy *et al.* misquote me as describing the study by the UK's Advisory Committee of Novel Foods and Process as "funny." To the contrary, I actually said this was the most serious critique of my work.

At the top of p. 985, Chassy *et al.* also make the assumption that in Table 5 of the original Feature, the average litter size is six pups and note that the "Wistar rat has a typical litter size of approximately 12." Again Chassy *et al.* have misinterpreted my experiments. The litter size was eight pups, not six. This is because 25% of the females from the group receiving GM soy didn't give birth, which was clearly indicated in my response to the question "How were behavior and fertility affected?" I wrote, "The number of pups per female was fewer than in the other groups (8 pups per female instead of 10–11 pups per female) and 25% of females didn't deliver pups at all. These results indicate that GM soy had a deleterious effect on the reproductive function especially of F_1 males, but also female rats."

Many of the above errors could have been clarified—had I been afforded the opportunity to respond. But the publication process for this article gave me no option to do so. I was not given the comments from Chassy *et al.* to read and respond to before publication. This meant that they spent much of their time raising questions about my work that could have been answered in a full paper. In my view, many of the inaccuracies and criticisms could have been avoided if Chassy *et al.* had been able to review a full scientific paper from me, rather than my responses to a limited set of questions. The scientific paper would have contained much more information.

I also have several serious concerns about other parts of the editorial process.

First, in e-mail exchanges between us, you refused to publish the whole text of my paper and moreover, when I submitted a paper containing new unpublished data to the journal, it was refused on the grounds that such a paper would be better published elsewhere. Yet, at the same time, *Nature Biotechnology* found it quite acceptable to assemble and publish a Feature which consisted of a brutal attack on my results.

Second, the galley proof, sent to me by the journal as a 'publication proof' had my name as the author and was vastly different from the article that appeared in print, omitting the introduction by you and the critiques from Chassy *et al.*

Third, the comments solicited were solely from researchers who I would regard as pro-GM, or with connections to the GM industry, who would likely be hostile to my work. Why were no comments solicited from scientists that have concerns about GMOs [genetically modified organisms]? The process and article were therefore not objective. Many independent scientists were unhappy with the format and their understanding of the commissioning process, and indeed sent me letters stating so.

And fourth, on the proof, many of my references in the original draft had also been removed. In the final published article, the comments of the pro-GM group included many references, potentially distorting the perception of my work as inferior and unsupported by the literature in comparison to the critiques.

I now turn to the critical comments concerning the publication of my research.

Chassy *et al.* ask if I "had external funding, why are we not told who provided such significant funding?" I could easily have provided this information, if it had been requested of me—but it wasn't. To clarify, I started experiments as an addition to my existing work and then included them as part of my regular research. Because I couldn't find evidence in the scientific literature of the effect of GMOs on the behavior of animals and their offspring, I decided to begin my own experiments. I also planned to try to use special GMOs to improve memory and learning in rats and for treating animals with diseases (such as epilepsy, Parkinson's disease and others). For my investigations, I used material and equipment at my institute, my own salary and a small amount of personal funds.

They also criticize me for failing to publish my work in the peer-reviewed literature and for widely publicizing my work at various congresses, meetings, press conferences and on the internet without providing sufficient experimental support for my claims. I would respond that I have already sent papers into peer-reviewed journals (one paper was submitted a year ago). And what they fail to acknowledge is the difficulty that I have encountered in publishing this work in the peer-reviewed literature—perhaps reflecting the reluctance of the predominantly industry-funded agbiotech community to condone the publication of studies that detail negative effects of GMOs. I am not against GMOs, but wish to promote more safe and effective approaches as much as I can.

When I started these experiments, I didn't expect that the work would attract so much interest. I only thought that scientists would repeat my experiments and confirm or refute my results. The wide interest in my work has not been confined only to investigations of the safety of GMOs, but has extended also to its implications for DNA and gene transfer, ecology and so on. I never sought out journalists. Every attack on me and my work by those allied to the biotech industry or by members of the media has served to create more interest from journalists, scientists, physicians and ecologists. After *Nature*

Biotechnology published the criticism of my work, I have received even more requests to give interviews and invitations to participate at different conferences and meetings.

I would add that I concur with Chassy *et al.* in that "science needs to be repeated and to stand the test of time." Most peer-reviewed articles containing evidence of negative effects of GMOs have been criticized and suppressed in much the same way as my own research. I feel this is because there is pressure to dismiss such studies because a huge amount of money has been invested in GMOs. All I have tried to do is to provide evidence of a potential problem with the safety of GM soy.

In 2005, I was concerned when I found the adverse effects of GM soy on rats and their offspring, particularly as the soy I used (Roundup Ready line 40.3.2) is widely eaten by people. I therefore appealed to the international scientific community to repeat my experiments with this GM soy and to extend such studies of other GM plants. In the ensuing 2 years, nobody has repeated this research completely, even though these experiments are easily repeated. However, I am not alone in identifying the adverse health and safety effects of GM products. The scientific literature also details the adverse effects of GM crops on insects[12–14] and mammals[7–9,15–17], as well as the presence of foreign DNA in the cells of adult animals and their offspring that have been fed a GMO diet[11,18–23]. Russian researchers performed similar experiments with protein-isolate of GM soy (RR, 40.3.2), showing negative influence of it on mice offspring[24]. I agree with those scientists of the opinion that these adverse effects could be imperfections in gene transformation methods[25–27]. I believe that it is possible to improve these methods, to make them absolutely safe for humans and the environment. Consequently, the adverse effects of GMOs demonstrated in my experiments deserve further investigation. Experiments like mine can only help to inform the biotech community of possible problems with their products that they may not be aware of so solutions can be found. In this context, I would be very grateful to receive samples of transgenic products from companies or other laboratories around the world for my ongoing investigations using rats.

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To the editor:

I am writing to express my outrage at the Feature published in your September issue and your unprofessional treatment of Irina Ermakova. Simply offering Ermakova the right of reply in a letter of correspondence is entirely unsatisfactory recompense for the deliberate and cynical damage that you have done to her good name.

This miserable business has distinct echoes of the sinister happenings of 2002, when your sister publication *Nature* published a peer-reviewed paper by Quist and Chapela[1] on GM-maize contamination, and then 'retracted' it, following sustained and intense pressure from the GM industry and from parts of the research community working on transgenic plants. That was an unprecedented and thoroughly distasteful episode that did immense damage to the journal's good name[2]. Afterwards, Philip Campbell, the editor, sought to justify his action on the grounds of a "technical oversight" by the journal that led to the "mistaken" publication of a "flawed" paper[3]. Now, this paper is heavily cited in the scholarly literature and its influence—and not just the matter of transgenes and Mexican maize landraces—have been considerable[4].

In the case of your September Feature, it is possible to identify (if one wishes to be charitable) a whole series of "technical oversights" which led you to publish an article authored by you and which would not have been out of place in the cheapest tabloid newspaper. I now ask you the following questions:

First, was it through a technical oversight that you allowed four of the best-known apologists for the GM industry to have free space in the pages of *Nature Biotechnology* for a premeditated attack on Ermakova, whose findings they happened to find distasteful?

Second, was it through a technical oversight that you connived with them to induce Ermakova to outline her findings in response to your questions, and then to publish their nonattributed responses? (I remind you that their comments were published as joint comments for which no particular person took responsibility and which were presumably not subject to a review process of any sort.)

Third, was it through a technical oversight that Ermakova was never told the names of the four men who were out to damage her reputation and was never shown their comments before publication?

Fourth, was it through a technical oversight that, according to the correspondence between you and Ermakova that she has shared with me, you clearly gave her the impression that this was to be 'her' article and then sent her a dummy proof (the only one she saw) which had her name on it as author?

This last point is possibly the most serious instance of editorial malpractice I have ever seen. I gather that you explain this away as a "mistake" in your office. I cannot accept that, and none of the scientists with whom I have

had contact has ever encountered such a blatant example of malpractice before.

If the above instances of technical oversight were indeed down to administrative errors within your office that does not say much for the efficiency and competence of you and your staff. If they were down to a deliberate and predetermined strategy to destroy the academic reputation of Ermakova—and that is indeed my interpretation—your continuing position as editor would become untenable.

Brian John

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To the editor:

We are writing on behalf of the Institute of Science in Society (London) to express our deep concern over your September Feature about Irina Ermakova and her work. The article is grossly unfair to Ermakova and certainly not in the best traditions of scientific publishing.

There are journals that routinely publish criticisms of papers along with the papers themselves. This can be an effective way of drawing attention to important but possibly controversial work, while not allowing it to go unchallenged. These journals generally adhere to some important rules. The target paper is written by the researcher(s); not by a journalist/professional editor. Comments from other scientists are published along with the paper, followed by a general reply by the author(s). Some of the commentators may be known to be critical of, or even hostile to the author's point of view, but the panel will include others who are not. That is quite different from what you have done.

You were wrong not to make it clear to Ermakova how you proposed to use her contribution, even to the extent of not showing her the proofs of what would actually appear in your journal. Such practice is more appropriate for a tabloid newspaper than for a serious scientific journal, and a public acknowledgement of the oversight from you is in order.

Mae-Wan Ho & Peter T Saunders

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To the editor:

I was very disappointed by your September Feature critiquing the results of Irina Ermakova, especially as I had previously considered *Nature Biotechnology* one of the best scientific journals in the area of biotechnology.

I feel that publishing selected extracts of Ermakova's results and experimental methods was inappropriate. These results should have been published as a full paper with a detailed description of the methods.

Presenting the work in this manner would have allowed everybody in the scientific world to assess Ermakova's methodologies and results. Indeed, the author herself feels that her data set does not give all answers and, due to limited resources, was constrained in what she could do. After publication of her paper, comments could have been invited from the scientific community, which could also have been published by the journal.

Publishing edited extracts of her work together with comments of scientists who are well known to uncritically reject even the notion that there may be risks associated with GM crops gives me the strong impression that your journal is politically motivated to (i) defend the dogma that there are no potential health risks associated with GM crops, (ii) destroy the reputation of scientists that dare to challenge that dogma and (iii) prevent such scientists from gaining the resources to continue their work on risks of GM crops and how to avoid them.

There are many analogies to the treatment that Arpad Pusztai received after he reported negative effects of GM crops on rats. His work was criticized without him being given a chance to defend himself or publish his work until much later. Also, he has until this date not been given the opportunity to repeat and/or continue his work and no one else was commissioned to repeat it either.

Your treatment of Irina Ermakova will confirm the views of many in civil society in the following two respects: first, you reinforce the idea that the scientific community as a whole is dogmatic rather than objective when it comes to GM crops; and second, that the scientific establishment tries to suppress data and rubbish scientists when they report data indicating risks associated with GM crops, rather than applying the 'precautionary principle' and doing further research to investigate the mechanisms underlying such phenomena.

I feel that the most honorable way forward for *Nature Biotechnology* would be to invite Ermakova to submit her results as a full paper to the journal, for the journal to select 'non-dogmatic reviewers' for the paper, and for the paper to then undergo the normal peer-review process. If the paper were rejected, Ermakova could be given clear indications as to why and how the issues criticized should be addressed. If she were unable to address the criticisms and do the extra experimental work as a result of the difficulty of getting hold of the materials (e.g., GM and near isogenic non-GM lines) because biotech companies refuse to supply her with them, then this could also be published by *Nature Biotechnology*.

Arpad Puztai was never allowed to repeat and do supplementary studies to address the criticisms of his work (and other laboratories were also not given the chance to repeat his work due to GM-crop materials and other resources not being made available). It would be a great shame if this were to happen again, particularly if one of the most respected scientific journals was implicated in suppressing such work.

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To the editor:

We write specifically about the process *Nature Biotechnology* underwent before publishing the September Feature on the work of Irina Ermakova. We are not writing at this time to debate the science discussed either by Ermakova or Bruce Chassy, Val Giddings, Alan McHughen and Vivian Moses. Instead, we are of the opinion that Ermakova should have been given a venue to present her data in full so that proper assessment could be made by the community. This would have avoided the obvious qualifiers made by the commentators because they did not have enough information at times. This kind of qualifier is annoying when normally it could have been raised during the peer-review process and corrected by the time the article went to print.

We would like to raise four specific points of concern about the editorial process for this article.

First, was the readership properly informed about the reasons you sought to publish Ermakova's results? In the feature, the editor seems to imply that *Nature Biotechnology* solicited comments

on Ermakova's text from other researchers after approaching Ermakova, when in correspondence described by GM Free Cymru the editor indicated to Ermakova that the request for her data came from a group of authors that had an interest in criticizing her work. If the latter is in fact correct, the readership might feel misled about your motivations for the Feature. *Nature Biotechnology* should not appear to be colluding with groups or individuals that have preformed views on a researcher or a data set, because we doubt that *Nature Biotechnology* would like to give the impression to its readers that a privileged few could organize an attack on a scientist with the collusion of the editor. It would be helpful to us if you were able to describe in full your motivations for your approach to Ermakova and the timeline of events.

Second, was it ethical and just treatment of Ermakova that she neither had the option to review the comments nor withdraw from your invitation? It is alleged that the article in proof form had her name as author, whereas the final piece has your name instead. This difference could reasonably have led Ermakova to the view that she would be able to present her story in the September edition, with the views of the four commentators and other community feedback in subsequent editions. That structure could also have left Ermakova with the impression that a larger audience than just the four commentators would be able to make fair input.

Third, it is alleged that Ermakova also did not see a proof of the article in a form that included either the comments or blank spaces into which the comments would later be placed. Was this the case? If so, has *Nature Biotechnology* done this at other times? If this allegation were true, we would suggest that some discussion is warranted on the appropriateness of this practice.

And fourth, was it ethical and just treatment of Ermakova that *Nature Biotechnology* provided her with no automatic right of reply to the critiques of Chassy *et al.* before publication, as has been alleged? In all other processes that we are aware of, authors of original science have an opportunity to reply to criticism. For example, if this had been a peer-review process, then the author could have disputed reviewers' remarks leaving it to the editor to draw his or her own conclusions or decide whether more reviews were necessary. It is highly unusual, and as far as we are aware unprecedented in *Nature Biotechnology* for the review reports to be published along with an article or for authors not to be invited to respond to a critical letter of an article and have the response and letter published together.

We are aware that some journals simultaneously publish articles and reviews, but that is not what Ermakova would have expected of *Nature Biotechnology*. Nor is that practice in any way comparable because those journals provide the author with space to make their complete and formal cases. *Nature Biotechnology*'s peer-review process also provides criticism in confidence. Although an author is not always given the opportunity to reply or rebut comments from reviewers, the author is also not required to publish an article just because it has been submitted. In this case, Ermakova does not appear to have been given an option to withdraw her text or reply to the commentators.

We understand *Nature Biotechnology*'s prepublicity policy and therefore reasons for not publishing an article with the data from the 2005 conference. It would have been laudable of *Nature Biotechnology* had this been an experiment with a quasi-peer-reviewed structure to properly bring information of great public interest back into the normal format of peer-reviewed publications. However, we are not left with confidence that in fact the motivation of *Nature Biotechnology* was to create a space for such work because you did not list this among your motivations.

Nevertheless, if the structure of this article is to be a normal or regular format for *Nature Biotechnology*, then we would recommend that you repeat it using existing unpublished feeding-studies from industry that a self-selected group of critics discusses without concern for a reply from the authors. We could probably provide you with a list of commentators who would be prepared to do this for you.

The research community tolerates the power of editors because they have earned the trust of the community. Although we may not like what you decide, we in the main know why you do or do not publish our work and can ruminate privately on the substantive issues raised by referees. However, the commissioning process for your Feature appears to be nonstandard in several ways that could potentially undermine the trust of the community.

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To the editor:

I am writing concerning the Feature that you 'authored' in the September issue.

I wish to point out that Irina Ermakova had no opportunity to respond to the criticism of your panel of 'researchers working in the field'. The lack of an opportunity to face those hostile comments lacks any sense of fundamental justice. Next, your researchers working in the field had not published animal feeding studies and their fields, like yours, were primarily public relations on behalf of the biotech industry. Furthermore, you have no 'neutral point of view' and should have sought a neutral person to put together an article. And, finally, you should have agreed with Ermakova as to the takeover and change of authorship of the article authored by her, as agreed in a publication proof!

Plagiarism (from the Latin, *plagiarus* meaning 'a plunderer', or an older term *plagium*, meaning 'kidnapping', or possibly *plagiare*, which is 'to wound') is the practice of claiming, or implying, original authorship of (or incorporating material from) someone else's written or creative work, in whole or in part, into one's own without adequate acknowledgement, according to Wikipedia (http://en.wikipedia.org/wiki/Plagiarism). On the basis of this definition, you seem to have plagiarized Ermakova's article by incorporating it into your article without first obtaining permission from Ermakova. You may be surprised to know that editors have no right to scoop up others' articles and incorporate them into their own or others' articles, without first obtaining agreement from the authors. If *Nature Biotechnology* is planning to promote plagiarism by editors as a general practice, you should inform the scientific public that you have moved in that direction.

The world requires that you should provide Ermakova a publication platform to reply to the critics of her work. Furthermore, I urge you to take time off, go back to the microbiology laboratory and reeducate yourself in the practice of full and truthful scientific reporting.

Joe Cummins

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Bruce Chassy, Vivian Moses, Alan McHughen & Val Giddings respond:

We limit our comments here primarily to the issues relating to Ermakova's experiments

and findings in the order in which she raises them in her letter.

Although Ermakova states that she received "soy clearly labeled as GM and non-GM soy," she still has not established the identity of the material tested, which is of paramount importance to an animal feeding study. The methodology and materials described by Ermakova are fatally flawed in several additional respects and as a consequence invalidate the experimental results. One of the basic issues is the content of the feed. The Archer Daniels Midland (ADM) catalog states and B.C. contacted ADM on October 20 and November 5, 2007, to verify that they do not sell—and have never sold—a 100% GM-soy product containing the RR-40-3-2 line to which Ermakova refers.

We must nevertheless apologize to Ermakova (and to readers) for any confusion that may have resulted from a typographical error in the statement she quoted from page 981—we can understand her confusion about our intended meaning. Our statement should have read: "the best that can be said is that commercial products sold by ADM would have been an indeterminate and variable mixture of conventional and GM soybeans." Our point was that commercial products not specifically labeled GMO free are unsegregated mixtures of numerous varieties of conventional and GMO beans; Ermakova therefore had no measure of how much GM content was fed to the animals. The market has many varieties, each of which has its own unique composition and properties. This is why it is necessary to ensure that comparisons are between isogenic or even near-isogenic varieties; comparison of like varieties is a prerequisite for animal studies.

The PCR results she reports in **Figure 1** do not demonstrate that the so-called GM soybean was 100% transgenic because Ermakova claims only that all samples (100%) of Arcon SJ tested positive by PCR. This is not the same as demonstrating that the positively testing sample is 100% transgenic soybean; all the samples might have had a small GM content so that all would have tested positive. It is essential to determine the percentage of GM-soybean content of the test materials both to allow others to attempt to replicate the procedures reported as well as to allow the actual exposure to GM-soybeans to be calculated.

Ermakova is comparing results obtained using different and uncharacterized soybean fractions. In one case, she fed ground soybean flour and compared that with results obtained using a protein concentrate (Arcon SJ). She refers to Arcon SJ as 100% transgenic soybean flour, which is incorrect; it is a concentrate, which is inconsistent with the claim that concentrates produced much less dramatic results.

There is also a much larger issue here: the composition of a sample of soybeans (or of any crop plant for that matter) is highly dependent on the location and conditions under which it was grown and harvested. Good practice dictates the cultivation of GM and non-GM soybeans in the same or adjacent fields to reduce soil and positional differences that might affect the composition. To overcome seasonal variation, the soybeans should be cultured in the same year.

It is of particular importance to note that isoflavone content varies between varieties, site of cultivation and growth year[1]. A point that we noted previously is that isoflavones have estrogenic activity that can dramatically affect the outcome of animal studies; neither was tested or controlled in her study.

As Ermakova thanks us for our detailed analysis of her work, we would also like to make the following suggestion. Guidelines describing the proper methods of preparing crop materials for animal studies were published this year by the International Life Sciences Institute (Washington, DC, USA) and are free online[2].

We thank Ermakova for clarifying that extra soy was provided to males and females during mating; however, we would be interested in her response to a more fundamental problem that we noted in the original article. In all of her experiments, she housed three female rats together and fed them animal chow and soy product in separate dishes. That experimental design does not allow one to measure how much soy and chow each animal consumed. This information is essential, without which no scientific conclusion can be drawn. As in the original Feature, we refer Ermakova to the internationally accepted guidelines for performing animal feeding studies published by the Organization for Economic Cooperation (OECD; Paris; http://www.olis.oecd.org/olis/2003doc.nsf/43bb6130e5e86e5fc12569fa005d004c/4502bee1ca16c943c1256d520028e259/$FILE/JT00147696.PDF).

Ermakova mentions that her protocol was different from that of Brake and Evenson[3]. Indeed, Brake and Evenson started with 18 animals and sacrificed them in groups of 3 over an 87-day period. Their protocol observed all international guidelines and norms and would have detected effects of the magnitude that Ermakova observed. Their paper can be used as a model of how to conduct a reproductive toxicology study: Brake and Evenson had a known field source of soybeans, reported the exact composition of the diet and, because they fed the animals a single preparation containing test or control materials and measured weight gain, they could have interpreted any differences in weight gain. No differences in weight gain and no pup mortality were observed by them. Brake and Evenson studied four generations and, contrary to Ermakova's claim, animals were exposed to soy throughout the life cycle.

Ermakova compared her animal study with human-based clinical trials. Humans are not genetically homogenous and as a rule produce results showing considerable variation. The inbred laboratory rat is quite the opposite of a human in this regard; it has been developed to perform studies that will result in small variances of the measured variables. It is not good practice to pool results from separate animal studies because individual lots of animals can and do differ, and reproducing diet and environmental conditions is difficult at best. Thus, results from animal studies are normally not pooled; instead, statistics derived from each group are compared. Doing so increases the variance of measured variables.

The numbers of animals used in the study and the means and variances Ermakova now report for the body weights of males and females do not correlate with the data she reported in Table 3 in the original Feature published by *Nature Biotechnology*. The data in the Feature showed a wide variation in weight gain for all three groups; the new means and variances she now reports cannot be produced from the original data in Table 3. In the Feature, Ermakova's three conclusions for the GM soy-fed rates she observed were: (i) higher pup mortality; (ii) lower weight gains; and (iii) poor reproductive performance. The current data seem to

contradict her original claim of reduced weight gain.

The weight gains reported in the controls are uncharacteristic of well-established literature averages for the Wistar rat. We interpret this as an indication of diet or environmental problems. Such wide variance in growth rates and the high control–death-rates are red flags signaling problems in experimental procedure.

The reporting of external variables that can affect behavior is good practice. The use of accredited facilities with standardized parameters not only ensures optimal health and development of the subject animals, it facilitates the comparison of results between experiments. We are still not sufficiently reassured by Ermakova's responses that environmental conditions were homogeneous throughout the animal facility where she carried out her experiments.

Ermakova now presents behavioral data from her feeding experiments, but doesn't mention if the studies were blinded. Because we still have serious concerns about the nourishment and treatment of the animals used, we cannot comment on her results. Ermakova's claims that GM soybeans have higher isoflavone notwithstanding, we cite published research demonstrating that, whereas soy isoflavone content varies considerably between varieties and harvests, GM soybeans have the same content of isoflavones as conventional soybeans[4,5].

In responding to our point in the Feature that several previous papers[3,6,7] contradict her results, Ermakova claims they "had a different aim…and thus they are not comparable." We respectfully disagree and do not see this as a basis for rejecting the feeding studies that we cited. These are well-conducted, peer-reviewed studies that exposed animals to diets containing a high content of soy or GM soy. Ermakova goes on to cite three papers from one group[8–10] that have reported adverse effects of GM soy on testes and livers. We feel it is important to stress here that unlike the studies we cited[3,6,7], the reports from Malatesta and colleagues[8–10] do not conform with established international standards and protocols and fail to document the source, the composition or the identity of the soybeans under study. But in contrast to Ermakova, these authors[8–10] are scientifically cautious about the biological significance of their observations. We suggest that readers compare the literature we have cited with the three papers to which Ermakova refers and make a judgment for themselves about the effects of GM soy.

Ermakova goes on to state she carried out the experiments under conditions that were "as close to natural" as possible and concedes that no evidence is available as to the cause of pup death. It is *pro forma* in animal studies to determine the cause of death. Laboratory animal studies are not intended to mimic nature. The white laboratory rat does not exist in nature: it was bred in a laboratory to be used in very standardized studies designed to reduce variability and minimize uncontrolled variation that might confound the results.

Ermakova contends that the Brake and Evans study[3], which contradicts her results, is not relevant because the feeding regime was "completely different" from the one used in her experiments, and suggests this is of significance because "only embryonic cells in the womb" would be affected by the EPSPS gene sequences, not the "sexual cells and/or organs before and during mating." As we note above, the whole-life, four-generational nature of the Brake and Evenson[3] study and its rigorous design cannot be disregarded. National and supranational regulatory agencies working in the public interest all over the world have examined extensive animal study data on GM soy and concluded it is as safe as, or safer than, conventional soy.

With regard to the data in Table 5 of the Feature: the litter size we computed from Ermakova's Table 5 as printed is that 12 dams produced 72 pups, which computes to six pups per dam, as we stated. A control group litter size value of eight does not improve the situation, because this is 50% below the normal litter size and a sign of animals in distress. With such high mortality and stunted growth, we must ask how normal reproductive experiments could have been performed with the GM soy-fed mice.

We leave Andrew Marshall to respond to the questions raised about the publication process, but we strongly object to Ermakova's characterization of us as 'pro-GM' scientists and in particular Brian John's slander that we are "apologists for the GM industry." It is a matter of public record that we declare no conflict of interest, save for V.M., who maintains a GM information website that does receive some funding from industry and L.V.G. who works as a consultant with some industry clients (none of which are involved in transgenic soy). Contrary to the correspondence presented here, the scientists with whom we have spoken and from whom we have received letters in regard to this matter have expressed their appreciation to us for trying to correct the misinformation contained in Ermakova's 2005 report. B.C., A.M. and V.M. are, or have been, university faculty whose mission is the apolitical and objective teaching of science. None of us characterize ourselves as 'pro-GMO' or 'anti-GMO' as a matter of philosophy. It is an issue on which we remain agnostic; rather, we characterize ourselves as 'pro-science', 'pro-environment' and 'pro-humanity'.

All scientific work can and should be subject to the full force of reasoned criticism. Ermakova's remarks that there is an industry conspiracy to criticize and suppress articles containing evidence of the negative effects of GMOs is refuted by Ermakova herself when she cites published work on GMOs (albeit flawed) that shows negative effects. Rather than a worldwide conspiracy, we deduce there are few publications showing harm because GM soy is safe and does not cause harm.

We conclude then, that Ermakova's research relied on experimental designs that fall short of internationally accepted norms, with animals handled in such a way that even control lines were negatively affected. The feeding studies used materials that were characterized inadequately, incorrectly or not at all. Thus, no scientific conclusions can be drawn from the work.

We must stress again that GM soy has been thoroughly studied in the peer-reviewed literature, by regulators around the globe and by the cruel testing place of the real world. More than 500 million hectares were cultivated over the past decade. Much of this has been fed at high concentration to domestic animals, poultry and fish. There have been no reports of stunted growth or reproductive failure as one might expect if Ermakova were correct.

COMPETING INTERESTS STATEMENT

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

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Andrew Marshall responds:

The September Feature was a new format for *Nature Biotechnology*. My aim in publishing this Feature was to provide an informative presentation of the science behind Ermakova's work, the problems posed by publicizing original data to the media without first publishing it in the peer-reviewed literature, and to open this particular debate to a wider audience. Indeed, many investigators who were unaware of her results now have an opportunity to build on her work and attempt to reproduce it. As I indicated to Ermakova in my original e-mail invitation to her (see **Supplementary Materials** 1 online), I felt that the biotech community would best be served if she had the opportunity to present her findings and conclusions in her own words—findings and conclusions that could not be published in *Nature Biotechnology* because of her decision to publicize them in other forums.

As *Nature Biotechnology* went to press, 20 letters had been submitted to the journal and several directly to the management of Nature Publishing Group concerning the format of this Feature and the process by which it was commissioned. Three letters applauded the journal for a useful and informative analysis of science that had been previously published without peer review. But the vast majority of letters were critical, repeating the points raised here by Irina Ermakova; we have printed above only those letters that present additional concerns.

There appears to be confusion about the way in which this Feature was conceived, commissioned and produced. There is a perception in some quarters that the Feature ultimately published in *Nature Biotechnology* is the same as a Commentary originally submitted to the journal by Val Giddings. This is not the case. I elected to decline to publish this original Commentary because the critique of Ermakova's work presented was based on data from publicly available sources, which may or may not have been reliable.

Ermakova's existing data were ineligible for peer-reviewed publication because she and others (including Brian John) had already promoted publicly the 2005 data before they received careful scrutiny in a peer-reviewed journal. She had distributed them widely in reports and discussed them with journalists. This contravenes our prepublication policy (http://www.nature.com/authors/editorial_policies/confidentiality.html). I strongly support this policy. Peer-reviewed publications are the places to publish scientific advances—not press releases, newspapers or postings on the internet. This prepublication policy is shared by all Nature journals and other top-tier science journals. This was made clear to Ermakova several times in our correspondence (see **Supplementary Materials** 1 online). As Bruce Chassy, Giddings, Alan McHughen and Vivian Moses (Chassy *et al.*) point out in the September Feature, and Stewart[1] has commented in our pages previously, circumventing peer review can have pernicious consequences for the public perception of science.

To provide readers with the most informative article on Ermakova's controversial work, I elected to go directly to her and asked whether she would be willing to describe her work in her own words and to pursue publication in the form of a Feature. My concept was to pose questions to Ermakova and then have a group of researchers respond to her answers. This was explained to Ermakova in the original commissioning e-mail (see **Supplementary Materials** 1 online).

Because of the controversy surrounding the work, I felt the readers would be interested in a presentation of Ermakova's results in the context of a scientific analysis. Including comments from established scientists was important because to my knowledge her results had not been presented in the context of a skeptical scientific analysis anywhere before.

A concern expressed in the Correspondence by Ermakova and in many letters received by the journal is that the researchers invited to comment on Ermakova's work did not comprise a representative sample of the broad range of views of scientists. On the contrary, Chassy, Moses and McHughen have established publication records, have thought deeply about Ermakova's results, are qualified to discuss their societal impact and can assess the data on the basis of established scientific norms. In drawing up his response, Chassy also consulted with an expert in the field of animal toxicology. In addition, Giddings is a recognized expert and consultant in biotech with respect to policy and regulations. I would also like to point out that contrary to Joe Cummins' assertion, I have no interest in, and never have been, in the field of "public relations on behalf of the biotech industry."

As Chassy *et al.* point out, a 'pro-GM' or an 'anti-GM' position is inherently unscientific. I wholeheartedly concur with this viewpoint. The safety and efficacy of any product should be assessed on a case-by-case basis, not according to the method by which it was produced. I am also struck that none of the correspondence elicited by the article has taken issue with the validity of the scientific criticisms made, only the identity of the authors who made them.

I sent Ermakova an initial set of 17 questions, to which she responded. These questions and answers were then forwarded to Giddings and Chassy, who conferred with Moses and McHughen. Their responses were appended to Ermakova's answers and I wrote an introduction explaining why we were publishing the Feature. In the galley proofs seen by Ermakova (**Supplementary Materials** 2 online), some questions had already been merged and one of the original questions ('What mechanisms do you think might underlie the health effects you observe in your study?') had been removed for conciseness and space constraints. During editing, I dispensed with the question and answer about mechanisms (question number 13 in **Supplementary Materials** 1 online) as I felt it was unnecessary and inappropriate to speculate on the mechanism of the defects reported by Ermakova, given the serious concerns raised by Chassy *et al.* over the rigor of the science and the design of the experimental protocol. It turns out that this question is the part of her original draft that contained the references she mentions were removed and gave the impression of her work as "inferior and unsupported by the literature in comparison to the critiques." Ermakova has now cited some of these omitted references in her letter above; for the rest of the originally cited papers, readers are referred to the list below[2–7].

Ermakova's other concerns related to the editorial process. She asks why I refused to publish new unpublished data from her laboratory, while at the same time assembling and publishing an article that is "a brutal attack on her results." This is conflating two separate issues, the journalistic criteria for publishing a Feature with the editorial criteria applied to selecting papers for peer review in the Research section. The Feature tackled Ermakova's original 2005 results because of their societal impact and the public attention they garnered when originally circulated widely over the internet and in the media. In contrast, research papers are selected by the journal's editors for evaluation by outside experts on the basis of whether the findings reported are novel, a significant advance over previous work and of sufficient interest to a broad audience. As stated above, Ermakova had disqualified her 2005 data from the

latter process by not conforming with our prepublication policy.

I indicated to Ermakova that *Nature Biotechnology* would be willing to consider any new data she had obtained, and I suggested she submit a presubmission enquiry to the journal. The presubmission enquiry was evaluated by one of our editors, who felt that the results would be better published elsewhere. Ermakova is still welcome to submit the full paper to us; however, promises of being selected for peer review are not made to authors at the presubmission stage. Publication of a journalistic Feature focusing on Ermakova's previous work cannot in any way influence decisions to send new research out for peer review, unless we deem it appropriate according to our editorial criteria for research papers.

Another point raised by Ermakova and by Brian John is that she was sent a 'publication proof' that showed her name as the author. This was a mistake made by *Nature Biotechnology* when generating the proofs, which I did not check before they were sent to Ermakova. Her name was mistakenly placed on the proof, which contained my introduction and her responses to my questions, but not the comments of Chassy *et al.* (**Supplementary Materials 2** online) The proof was thus much different from the form we had discussed for the final published article (containing comments from other scientists). Clearly, this was confusing and led Ermakova to believe she would be the sole author of the piece.

I accept full responsibility for not reconfirming with Ermakova what I had explained in my original e-mail to her, that her responses were to be part of a larger Feature, *and* that I would be the author of this journalistic piece. Again, I believe many of the misunderstandings here have arisen due to a wrong perception—both by Ermakova and other correspondents to this journal—that the September Feature is a peer-reviewed research paper, rather than journalistic content.

Ermakova's charge that she never saw the final remarks of Chassy *et al.* or my introduction to the article also reflects a misunderstanding of the publication process for content that is not peer-reviewed research. The Feature we were preparing on Ermakova's work was intended to be a journalistic Feature for the magazine section of *Nature Biotechnology*. Like other purveyors of news content who conduct interviews and then publish articles based on the content, there is no precedent for revealing the names or comments of the other contributors to an article. This is standard practice for *Nature Biotechnology*, other Nature journals and for journalistic content in general. In these circumstances, it is the editor's responsibility to faithfully reproduce the remarks made by the interviewed parties.

There are several take-home lessons from this first experience, if *Nature Biotechnology* were to repeat this unusual format in the future. We will do a better job ensuring that all authors grasp the process from the start, including authorship and issues surrounding comments made in any interviews. Although I regret that Ermakova misunderstood our publication process, at no time did I indicate that she would be given full authorship of the Feature or that she would see the critiques of the researchers or learn their identities. The key e-mail correspondence between Ermakova and me is presented in **Supplementary Materials 1** online so readers can make up their own minds about the quality of the communication process.

In the future, it would be better practice to ask single scientists with particular expertise to respond to different questions rather than publish their comments as a group. In the format published in the September Feature, the comments from Ermakova were appended with collective comments from Chassy *et al.* In his letter, John raises the point that no one takes "full responsibility" for collective responses. This is one aspect that many of our correspondents found particularly distasteful.

With hindsight, a more thorough editorial effort should be undertaken to ensure that authors whose work is being commented upon have sufficient opportunity to respond to criticisms that are based on insufficiency of data provided. Although I had asked Ermakova to show more behavioral data in response to questions raised by Chassy *et al.*, several other comments in the published text criticized her for not providing other data, to which I gave her no opportunity to respond. That said, Ermakova has now had a full opportunity in these pages to respond to all the comments in full.

I would certainly welcome feedback from readers as to ways in which this Feature format could be improved in the future. One question is whether it is appropriate for a journal to allocate pages in the form of a full research article (as Leifert, Traavik and Heinemann suggest I should have done for Ermakova's experiments) when the primary criteria for editorial selection is the unusual societal and regulatory impact of the work, rather than its scientific quality or impact. Perhaps one solution for such papers would be for their listing on prepublication servers that allow community comment in an open manner and in a neutral environment (e.g., *Nature Precedings*, http://precedings.nature.com/). Unlike public release in the media, this would not preclude later publication in a journal. I invite readers to make suggestions for ways to present work that has circumvented the traditional peer review process but is nevertheless of interest to the wider research community and public.

Note: Supplementary information is available on the Nature Biotechnology website.

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