GM soybeans and health safety—a controversy reexamined

Andrew Marshall

An unprecedented study claiming that transgenic soybeans compromise the fertility of rats and the survival and growth of their offspring has garnered widespread media and political attention but remains unpublished in the peer-reviewed literature. Here, an account of the work from the principal investigator, Irina Ermakova, is appended with comments from researchers in the field.

Neuroscientist Irina Ermakova of the Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences in Moscow made news headlines two years ago when she reported that rats fed diets containing glyphosate-tolerant genetically modified (GM) soybeans gave birth to pups with low survival rates or stunted growth[1]. Though these findings have yet to appear in a peer-reviewed journal and contradict publications in the literature, they have been widely disseminated and discussed over the media and internet and already cited by >500 organizations as evidence of the potential toxicity of GM products. They've also prompted the American Academy of Environmental Medicine (Wichita, KS, USA) to call for additional independent studies of food safety for GM crops[2], been referred to in a state Australian parliamentary debate as a reason to ban GM crop cultivation[3] and motivated regulatory agencies in several countries to review their approvals of GM organisms or to comment on the work[4,5].

Nature Biotechnology approached Ermakova to ask for a detailed account of her work in her own words. Her answers are presented below together with comments solicited from a group of researchers working in the field.

Irina Ermakova, the author of controversial studies reporting soybeans genetically modified for resistance to glyphosate may be dangerous to newborns, agreed to provide details of her work to *Nature Biotechnology*.

Briefly describe your experimental design and methods.

Irina Ermakova. My experiments were designed to study the influence of a diet containing genetically modified (GM) soybeans (Roundup Ready (RR) line 40.3.2) on the physiological state and behavior of Wistar rats and their offspring. In addition to laboratory chow, one group of female rats was fed soy flour or seeds for 2 weeks before mating, during mating and pregnancy, and was fed an increased daily amount for every pup during lactation. At the same intervals, a second group of female rats receiving chow was fed conventional soy flour or seeds and a third group received protein isolated from RR GM soy. A fourth group of rats received only the laboratory chow and was considered to be a positive control. We analyzed the physiological state (weight, size and so forth), reproductive functions, rate of mortality and behavior of rats and their offspring. Experiments were repeated five times using soy flour, soy seeds, standard chow and chow mixed with GM soy (~14%) in different groups of rats.

Standard chow contained wheat, wheat bran, sunflower, meat flour, animal fat, barley, fodder yeast, microelements and vitamins. RR soy flour genetically modified with the transgene 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) obtained from *Agrobacterium* sp. strain CP4 (Monsanto; St. Louis, MO, USA), its protein isolate and conventional soy flour (Arcon SJ 91-330), which has a similar composition and nutritional value to RR GM soy, were obtained from the Netherlands supplier of Archer Daniels Midland (ADM; Decatur, IL, USA). Analysis of soy flour by PCR showed the presence of the EPSPS transgene in all samples of RR GM soy.

The chow was administered as dry pellets from a special container placed on the top of their cages and the (GM, GM protein isolate or conventional) soy flour mixed with water (20 g soy paste in 40 ml water) in a small container placed inside their cage for three rats. Each rat thus received 6–7 g flour every day. A similar scheme was used for soy seeds, which were kept in water for 1 day before feeding and then put into a small container inside the cage: four seeds for one female and six seeds for one male.

Bruce M. Chassy, L. Val Giddings, Alan McHughen and Vivian Moses. Ermakova states that RR soybeans and protein isolate were purchased from ADM in the Netherlands. ADM does not sell (and has never sold) pure 100% RR soybean preparations. It is accordingly not possible for Ermakova to have obtained RR soybeans from this source as stated. 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. These most likely would also have comprised a mixture of commercial soybean cultivars rather than a single cultivar. ADM does supply identity-preserved non-GM soybeans; however, most of these too would be mixtures of non-GM cultivars. It is standard practice in feeding studies of this kind to compare the responses of test animals fed the GM variety with those

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Bruce Chassy of the University of Illinois at Urbana-Champaign says Ermakova's work illustrates the need for the public and media to be cautious of scientific claims that have not been reproduced or passed the rigor of peer review.

fed a conventional variety with similar genetic background (near-isogenic control).

Ermakova also indicates that Arcon SJ was fed to one control group of animals. She describes the material as a "GM-free" soy flour with a composition equivalent to RR-soybeans. The ADM product catalog states that Arcon SJ is a soy protein concentrate that contains 70% protein (as opposed to 40–45% protein found in soybeans). Arcon SJ is not nutritionally equivalent to soy flour. Ermakova provided no PCR evidence that the Arcon SJ product did not contain the CP4 EPSPS 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.

In feeding studies of the kind reported by Ermakova, it is essential to determine the nutritional composition of test and control diets and to show that each provides balanced and equivalent nutrition. In addition, the content of soybean antinutrients (e.g., trypsin inhibitors) should be determined to establish equivalency because these can affect the outcome of studies. It is of particular importance to measure the isoflavone content as differences in this pseudo-estrogenic component could affect mating, reproduction and growth, as well as other parameters[6]. The inaccurate description of materials used in this study and the lack of data regarding diet composition fail to meet minimum standards for animal studies.

The rats were fed chow (apparently *ad libitum*; see below) and soy preparations were supplied separately as an aqueous paste at a rate of 20 gm/3 rats. No data are supplied on individual consumption by each rat. In this kind of study, animals are normally caged individually, the test material is typically incorporated into the chow and the chow consumption of each animal is noted every day. Using the multiple animals/cage design described by Ermakova, animals could have consumed soy or soy-derived ingredients in an amount ranging from 0% to 100% of their daily intake. It is therefore impossible to determine either the food intake or soy exposure for any of the animals in the study (dams, sires and pups). Ermakova states that males were not exposed to soy; however, they were placed into cages with females to which soy was provided every day. After 3 days, the males were moved to the cage of another female where they remained for three additional days. No precautions were taken to exclude the possibility that males could consume some of the soy test material intended for females and thus the males would have been exposed to soy, GM and/or non-GM. Consumption of soy by males would have also reduced the ration of soy available to the females.

Several internationally accepted standard protocols for animal testing could have been followed by Ermakova in the design of the feeding and data collection procedures of this study[7–10]. These protocols have been developed to ensure the conduct of valid studies that will be acceptable to the scientific community, including regulatory agencies. Studies that do not record the exact dietary composition and intake amount for each animal, including exposure to test substance, lack scientific validity.

How many animals were studied and how many experiments were pooled into your final results?

I.E. We repeated the experiments five times with different groups of animals and with the four RR GM soy supplementations (that is, GM flour, GM seeds, protein-isolate GM soy or chow with GM soy). Rats in control groups received conventional soy (as flour or seeds). In the first three repeats of the experiments, 30 females, 40 males and 221 pups were investigated. In total, for the five repeats of the experiments, we examined 48 females, 52 males and 396 rat pups. Similar results were obtained in all the different repeat experiments.

B.M.C., L.V.G., A.M. and V.M. Results from independent, but identically designed animal studies can be used to evaluate the reproducibility of an effect, but it is not standard practice to pool data from such studies due to potential differences in factors such as diet, housing conditions and variability between batches of animals. 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 approximately 5 for each experimental group. Although some types of feeding studies can be performed with as few as 10 animals/group, standard protocols for reproductive toxicology studies typically commence with 20–25 animals[7–10]. It can be expected that the results from five trials performed with fewer animals will exhibit greater variability than a single large-scale trial that employs the same number of animals.

How were the animals housed and observed during the study?

I.E. Rats, weighing from 180 g to 200 g, were kept in a vivarium with a reversed light-dark cycle (12 a.m. to 12 p.m.). Each day, females and males in every cage received dry pellets from a special container placed on the top of their cage. Animals were also provided with 200 ml of drinking water per rat per day. After 2 weeks on the different diets, three females from each group were mated with two healthy males of the same age, who had not been exposed to the soy flour supplements. First one male was placed with a female in the cage for 3 days, and then another for 3 days. To minimize infection risk to females, invasive tests to determine sperm count and quality were not determined. Upon delivery, all females were transferred to individual cages, and the amount of soy supplement was increased by an additional 1 g for every pup born. Laboratory chow and water were available *ad libitum* during the experimental period, for all animals. When rat pups could feed themselves, the daily dose of soy supplement was increased to 2–3g for each pup. All rats ate their soy portions well.

Former Biotechnology Industry Organization (BIO; Washington, DC, USA) staffer and industry consultant L. Val Giddings believes Ermakova ignored the standard scientific practice of submitting research for peer review before publicizing her results.

B.M.C., L.V.G., A.M. and V.M. Ermakova notes that the ration of soy supplement "was increased to 2–3 g" per day when rat pups could feed themselves and adds that "all rats ate their soy portions well." Setting aside the fact that the statement may indicate that the normal ration was inadequate to meet the animals' needs, quantitative intake is again not reported. What's more, it is not clear whether pups were weaned and removed from the dams. It is also not stated whether the litters were balanced with regard to number of pups and gender. It is normal practice to compare results from litters adjusted to equal size (usually eight pups, four females and four males) to avoid differences in nursing.

What methods were used to assess animal health and behavior?

I.E. Adult animals were weighed before feeding and 2 weeks following commencement of the feeding experiments. Weights and sizes of pups from the different experimental groups born at the same time (±1–2 days) were recorded 2 weeks after birth. We also determined the weight of some internal organs (e.g., brain, liver, spleen, heart, lungs, kidneys and testes) and analyzed the morphology of the liver and testes. We examined the explorative behavior in the open field, determined the level of anxiety using a light/dark test and observed rat behavior in home cages.

Behavioral experiments were performed with male and female rats 2 weeks after commencement of feeding and when pups were 2 months old. All experiments were conducted in the second half of the day when rats were more active (starting at 5 p.m.). Each group usually contained 9–10 animals. The open field test was represented by a round platform, 100 cm, in diameter divided into zones restricted by sector rays and concentric circles. The platform was surrounded by a wall, 30 cm high. The center of the open field was illuminated by a frosted bulb (40 W). The session was conducted in a sound- and light-proof room. A rat was placed in the center of the open field and the number of horizontal translocations, vertical positioning, grooming, number of boluses (defecation) and freezing were recorded over 6 min. For each parameter, the relative value of extinction was estimated as the following ratio: difference in activity between the second and the first 3-min intervals divided by integral activity. The level of anxiety was investigated using a light-dark test (Intertex, Multiscreen) for 5 min. This model included two boxes: dark and light (four 3.5-W lamps). The number of rat entries into the light box, time spent in the light box, duration and number of instances of rat rearing on hind legs in the light box, the latency before a rat first entered the light box, the number of times a rat looked out from the dark box, urinations, defecations and grooming were all recorded.

The University of California's Alan McHughen thinks that there are critical problems with Ermakova's experimental design and research techniques that throw doubt on the validity of her conclusions.

We analyzed the level of mortality in each of the test groups using one-way ANOVA verified using Newman-Keuls share distribution test. Pup weight was analyzed by Mann-Whitney and its distribution by Chi-square using StatSoft (Moscow) Statistical version 6.0.

B.M.C., L.V.G., A.M. and V.M. 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. Normally weights are compared at weaning (3 weeks). This makes comparison with literature values difficult.

There are several difficulties with the behavioral studies as described. It is not clear that these experiments were performed in a double-blinded manner and, given the apparent differences in size and vitality between the groups, it is hard to imagine that handlers could not distinguish between the groups and would thus lose their objectivity. In addition, 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. Explicit, operationally defined scales for each measure of the battery is to be employed in the study should have been provided[11,12]. No actual data from behavioral studies are presented. We are therefore being asked to accept the subjective anecdotal claim that soy diets affected behavior. Taking into account the deficient experimental design, and signs of poor animal husbandry and unbalanced nutrition—as judged by high control-group mortality and poor growth performance—it should come as no surprise that deficient animal stewardship would lead to behavioral changes.

Briefly describe the main findings from your study.

I.E. Our data demonstrate a high level of mortality in pups born to mothers receiving RR GM soy–supplemented diets during the 3 weeks following birth compared with pups from control groups over the same period. Many (more than one-third) of the surviving pups born to mothers receiving GM soy had a stunted size and low weight compared with pups born to mothers from controls. A similar number of pups were born to mothers receiving GM soy, traditional soy and control groups (10–11 pups per female) but fewer pups were born to rats receiving soy protein isolate (8 pups per female). Behavioral studies indicated a high level of anxiety and aggression in males, females and young pups fed on the different groups GM material. Morphological analysis of internal organs indicated marked pathological changes in the blood supply to testes and vacuolization in the livers of male rats fed GM soy seeds. We also failed to breed second-generation (F_2) pups from matings of first-generation (F_1) females and males fed material based on GM soy.

According to the University of London's Vivian Moses, in the context of published peer-reviewed studies—as well as more than 10 years of real-world use of RR soybeans and the products derived from them—the claims of Ermakova seem implausible at best.

B.M.C., L.V.G., A.M. and V.M. No objective behavioral or morphological data are presented. Claims should not be made without presentation of evidence. Previous reports in the literature have shown no effects of RR soy on birth weights or pup mortality[13,16,17]; they have also not shown any effects of RR soy on the testis or in the livers of male rats fed RR soy[13,16,17]. What is more unusual, no methodology is given nor data reported for Ermakova's claimed measurement of testicular blood flow, an endpoint that is not routine in rodent toxicology studies. Ermakova's claim that mating was not possible in second-generation (F_2) males as a result of GM soy exposure contradicts a previous study[13] that found no reproductive effects in mice in a multigenerational feeding study with RR soy.

What was the level of mortality of the pups you found in the control and test groups?

I.E. In first three repeats of experiments, up to five times higher mortality was observed in newly born pups whose mothers had received the GM soy flour supplementation compared with pups from rats receiving GM soy protein isolate, traditional soy or laboratory chow (controls) (see **Tables 1** and **2**). Pups from rats that had been fed a GM soy diet died mostly during the 3 weeks following birth; pups from rats fed laboratory chow (positive control) died during the 2 weeks postpartum; and pups from those fed traditional soy died during the first week after birth.

Table 1 Mortality of rat pups by the end of the 3rd week of lactation

Groups	Number of newborn pups	Number of dead pups	Dead pups/total born (%)
Control	74	6 $P < 0.001$[a]	8.1%
GM soy	64	33	51.6%
GM soy protein isolate	33	5 $P < 0.01$[a]	15%
Traditional soy	50	5 $P < 0.001$[a]	10%

[a]Compared with the GM-soy flour–supplemented group.

B.M.C., L.V.G., A.M. and V.M. Pup mortality is usually reported at day = 0 or day = 1 and day = 21. The timing and causes of death are not reported. The data in **Tables 1** and **2** show that 8.1% of pups died in the control group. The typical mean pup survival observed for Wistar rats is greater than 99% ± 2 at day = 1 and 99.5% ± 1 at day = 21 (ref. 14). The abnormally high incidence of pup mortality in the controls indicates poor animal stewardship possibly arising from poor animal husbandry and/or dietary deficiency. No valid scientific conclusions can be based on a study with such a poor performance in the control group. **Table 1** also reports 10% mortality on conventional soy; no conclusions should be drawn from a study in which the conventional soy control mortality is tenfold higher than that normally observed for Wistar rats. The details of the post-mortem examination of pups are not reported and no cause of death is offered for the observed high incidence of pup mortality.

The claim of 51.6% pup mortality in GM soy-fed groups defies credibility. It is not possible that such a strong lethal effect could have evaded researchers, regulatory agencies, health and agricultural agencies and animal producers for more than a decade. The more likely explanation for the observed health effects is poor experimental design and conduct as demonstrated by the exceptionally high mortality observed in the controls.

What was the weight of the control and test group animals?

I.E. We did not find any significant differences in the weights of adult rats fed the different diets in two weeks after beginning of feeding. Even so, for 2 weeks following birth, the weights of pups from mothers fed GM soy supplement were lower than those of pups from rats in the positive control (laboratory chow) group or from the conventional soy flour–supplemented group. We also found that 33% of pups from rats fed GM soy had smaller sizes and lower weights than pups from rats fed laboratory chow, traditional soybeans or soybean protein isolate (**Table 3**). A crude anatomical analysis revealed that the organs of pups from rats fed GM soy were much smaller and weighed less (except the brain mass) than those from pups born to rats fed other diets (**Table 4**). Thus, age-matched pups in the test and control groups show differences in the development of internal organs.

B.M.C., L.V.G., A.M. and V.M. Animal weights are normally recorded for individual animals in a litter and then averaged as mean for females and mean for males to account for gender differences. **Table 3** does not segregate animals by gender, despite the likelihood of males being ~2–3% larger than females at this age. More importantly, under carefully controlled conditions, 14-day pup weight (~38g ± 3g) will vary by no more than ±10% (ref. 14). The data in **Table 3** are presented in an unconventional manner that makes it difficult to determine the exact mean and standard deviation among groups. **Table 3** states that 53% of control pups are below 30 g, which is abnormally small for two-week-old Wistar rat pups. More than 90% of rat pups fed conventional soy are >20% below normal weight; GM soy (79% below typical weight) and GM soy protein isolate–fed pups (78% below typical weight) fared somewhat better. The wide variance of data in **Table 3** and the high percentage of low-weight animals are clear indicators of malnutrition and/or poor environmental conditions. No conclusion can be made about abnormal development unless the controls conform to internationally observed norms.

Table 4 reports "examples" of body and organ weights (with no units specified). Means are normally reported for all the animals in a control or experimental group and the values are normalized to both body weight and to brain weight. As presented, **Table 4** is meaningless.

Table 2 Comparison of different kinds of chow on rat pup mortality[a]

Groups	Number of pups born per female	Number of pups born	Number of dead pups	Dead pups/total born (%)
Usual chow	~ 11	74	6	8.1%
Chow containing 14% GM soy content	~ 10	72	24	33.3%
Usual chow plus GM soy	~ 11	64	33	51.6%
Chow containing 14% GM soy content plus GM soy	~ 10	89	46	51.7%

[a]By end of the 3rd week of lactation.

How were animal behavior and fertility affected?

I.E. Behavioral experiments showed very slight differences between groups in open field test. Even so, both anxiety in the 'light-dark' test and aggression were higher in females, males and offspring receiving GM soy in their home cages than in rats from other groups. Aggression was more frequent in females and pups; not only toward one another, but also toward the laboratory personnel caring for them. Some (~20%) of the females, fed by GM soy, failed to care for their pups (instead scattering them around the cage without nesting). For rats fed GM soy, we failed to breed second-generation pups from F_1 males ($n = 24$) and females ($n = 24$). In marked contrast, the crossing of F_1 females ($n = 12$) receiving the GM soy diet with F_1 males ($n = 12$) from the positive control group (laboratory chow) resulted in 72 pups (**Table 5**). Even here, however, 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.

B.M.C., L.V.G., A.M. and V.M. The results reported in **Table 5** are unique and without precedent in whole food feeding studies with rats. Although no objective behavioral data are presented, a total failure of adult animals to produce offspring would be remarkable. It is not clear whether the animals failed to achieve estrus, whether they mated but were infertile or whether pregnancy was aborted. The more significant problem with the data as presented is that there are no data for conventional soybeans. There is no way to determine if soybeans *per se* produced this effect or whether

the effect is restricted to GM soybeans. We would be skeptical of the latter claim.

We find the claim (**Table 5**) that 12/12 dams fed non-GM soy produced a total of 72 pups whereas none of the GM-soy fed groups produced a single pup, even less plausible when we consider Ermakova's previous reports. The Wistar rat has a typical litter size of approximately 12 ± 1 (ref. 14), whereas in **Table 5** the average litter size is six pups. This is a clear caution flag of poor animal health, nutrition and/or stewardship. On her website (http://www.irina-ermakova.by.ru/eng/articles.html) and in published conference proceedings[1] Ermakova reported a gestation rate of 73.3% (11/15 dams), with control, soy fed and GM soy fed groups having comparable fertility. These numbers are far below the gestation results typically observed for Wistar rats (>98.5%), which once again points to poor stewardship[14]. These numbers are also inconsistent with the present claim of 100% fertility in control groups. It is remarkable that such a strong effect would be seen in the F_1 generation whereas no effects were noted in comparably treated dams of the F_0 generation. We are at a loss to explain these sudden changes in reported fertility.

Table 3 Distribution of weights of pups in 2 weeks after birth

Groups	50–40 g	40–30 g	30–20 g	20–10 g
Control	8.2%	38.8%	40.8%	12.2% ($P < 0.05$)[a]
Traditional soy	0%	9.7%	77.4%	12.9% ($P < 0.05$)[a]
GM soy protein isolate	0%	21%	72%	7.0% ($P < 0.05$)[a]
GM soy	0%	26%	40.7%	33.3%

[a]In comparison with GM soy.

What do you conclude from your findings and what are your plans for future research?

I.E. As it is well established that raw soybean contains several antinutrients (e.g., lectins and trypsin inhibitors)[1] and female hormone-like substances (e.g., phytoestrogens), our experiments both used a positive control (laboratory chow alone) and fed rats experimental and control diets 2 weeks before mating, during mating, through pregnancy and until the litters were weaned. The very high rate of pup mortality in litters of mothers on a diet supplemented with RR GM soy flour was very unexpected. The lower weight of surviving pups from rats receiving GM soy was also notable, particularly because the higher mortality resulted in (~50%) smaller litters, which should have doubled the amount of milk available. These pups should have had a better chance to grow than pups from other groups with larger litters, unless the amount and/or the quality of the milk is deleteriously affected by consumption of GM soy flour.

We concluded that RR GM soy appears to have a strong negative influence on Wistar rats and their offspring, causing high levels of pup mortality, infertility in surviving pups, decreased weight gain and size in some pups, pathological changes in internal organs and deleterious effects on behavior. My opinion is that GM soy's effect on Wistar rats and their offspring should be relevant to all mammals, including humans.

It would have been instructive to compare the effect on rats and their offspring of RR GM soy with another GM soy line or with a completely different kind of GM plant. I hope to perform these experiments in future. We plan to compare the influence of different GMOs [genetically modified organisms] (not only RR soybeans) on the physiological state and behavior of rats and their offspring. We are also planning to analyze the reason of pup's death and attempt to detect the presence of foreign DNA in white blood cells, brain, liver and other internal organs of adult animals and pups.

B.M.C., L.V.G., A.M. and V.M. In contrast to Ermakova, we conclude that no meaningful inferences can be drawn from these results. The experimental design does not follow internationally recognized protocols that were developed to guide researchers in proper design[7–10]. The nature of the source material is unknown, the consumption by each animal is unknown and the composition of the diet is unknown. Too few animals were studied and gender differences were not recorded. The abnormally high mortality and low growth rates of the control groups point to poor animal stewardship.

Considering the control results were consistently outside of the range of norms observed for Wistar rats, we have broader questions as well. Is the animal care facility in which these experiments were done a certified facility that meets contemporary standards, such as those described in the guide published by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC; Frederick, MD, USA; http://www.aaalac.org/resources/theguide.cfm)? Were all conditions in the environment appropriately controlled?

It is also of concern to us that Ermakova appears never to have published a peer-reviewed paper describing an animal study of this kind nor does training for such studies appear to be in her academic background. We are not suggesting that trained investigators cannot teach themselves to perform a proper study, but this lack of prior experience may explain why Ermakova failed to heed published international protocols for laboratory animal studies (or was unaware of them). It is noteworthy that, like Ermakova, none of us has performed or published a reproductive toxicological animal study. We have educated ourselves on the proper performance of such studies by reviewing the literature and the readily available standard protocols[7–11,13,14,16–19]. It has been reported that animal studies cost $300,000–$845,000 (ref. 15). Did Ermakova have the required level of funding and resources to carry out the experiments judiciously? And if she had external funding, why are we not told who provided such significant funding?

Last, but by no means least, the adverse effects on reproduction, survival and growth rate observed by Ermakova when RR soybeans are combined in animal diets contrast sharply

Table 4 Examples of absolute values of organ mass[a] in pups 3 weeks after birth

Experiment	Body	Liver	Lungs	Heart	Individual kidney	Spleen	Testes	Brain
Control	69	3.80	1.20	0.37	0.44 and 0.44	0.52	0.34/0.34	1.67
Control	72	4.63	1.55	0.38	0.52 and 0.42	0.81	0.3/0.3	1.60
GM soy	35	1.83	0.6	0.19	0.28 and 0.28	0.21	0.13/0.14	1.60
GM soy	30	1.68	0.5	0.20	0.2 and 0.19	0.19	0.14/0.18	1.54
Conventional soy	62	4.28	0.95	0.36	0.38 and 0.38	0.24	0.22/0.26	1.76
Conventional soy	63	4.35	0.94	0.39	0.42 and 0.42	0.32	0.23/0.22	1.66
GM soy protein isolate	63	3.71	1.04	0.47	0.44 and 0.44	0.36	0.2/0.19	1.62
GM soy protein isolate	63	3.46	1.42	0.41	0.43 and 0.33	0.38	0.23/0.24	1.74

[a]Organs fixed in formaldehyde, 0.1 M PBS, pH 7.2.

Table 5 Success of mating of first-generation (F_1) offspring receiving GM soy

Females (number)	Males (number)	GM soy feeding scheme	Mating scheme	Number of rat pups F_2
12 F_1	12 F_1	Continuation of GM soy additives for females and males	3 females × 3 males (in turn) $n = 36$	0
12 F_1	12 F_1	Feeding by GM soy was stopped before mating for females and males	3 females × 3 males (in turn) $n = 36$	0
12 F_1	12 controls (from mothers that didn't receive any soy additives)	Stopping of GM-soy additives before mating for females	3 females × 3 males (in turn) $n = 36$	72

with the results of all previous studies. Brake and Evenson[13] conducted a multi-generational feeding study in which mice were fed a diet containing glyphosate-tolerant soybeans. These authors observed no differences in litter size over four generations between mice eating a diet containing 21% RR soy versus conventional soy. Most notably, and markedly different from what Ermakova reports, Brake and Evenson state "in all generations we noted no deaths of the progeny." In other studies where rats and mice were fed meal from conventional and RR soy for 15 weeks at dietary levels of 30% by weight, there was no evidence of any changes in survival, growth, food consumption, organ weights or histological appearance of tissues in animals fed RR soy soybean meal compared with those fed conventional soy[16]. When rats were fed meal from conventional soy and RR soy (up to 90% of the diet by weight) for 13 weeks, no evidence was obtained of reduced survival, growth retardation, changes in clinical pathology or microscopic appearance of tissues[17]. Neither was any difference observed in the growth of young rats, catfish and chickens that were fed GM glyphosate-tolerant soybeans in the diet for 4 to 10 weeks[18]. None of these studies reported unusual mortality or changes in growth rates in the presence of RR soybeans. Finally, in a study involving swine, which have cardiovascular and digestive systems more similar to humans than rats, no evidence has been found for growth retardation or reduced survival when RR soybeans are added to the diet[19].

Do you feel that the translation/interpretation of your work has been accurate?

I.E. My experiments were published first in Russian and then in English. There were several incorrect (some even funny) interpretations of my work. One of the most serious critiques was published in the "Statement on the effect of GM soy on newborn rats" from the UK's Advisory Committee of Novel Foods and Processes (ACNFP; London)[20]. The Committee compared my research with only one (!) published article by Brake and Evenson[13]. But my study is not comparable with the work by Brake and Evenson for several reasons. First, the focus of the two investigations was completely different. Our experiments analyzed the effect of GM soy on mortality, physiological state and behavior of pups; in contrast, the studies of Brake and Evenson investigated the effect of GM soy on fetal, postnatal, pubertal and adult testicular development. Second, we used several different schemes of feeding; we commenced feeding 2 weeks before mating, which suggests that foreign genes ingested by these animals can penetrate and affect the sexual cells and/or organs. In the experiments of Brake and Evenson "pregnant mice were fed a transgenic soybean or a nontransgenic (conventional) diet through gestation and lactation....Multigenerational studies were conducted in the same manner." Thus, in their study, foreign genes could influence only embryonic cells in the womb and not sexual cells or organs before and during mating. And third, Brake and Evenson used only a very small number of pups in their study: "At each point, three male mice were killed, the testes surgically removed and the cell populations measured by flow cytometry." And they also mated a smaller number of animals: "Two C3H/HeJ males and two C3H/HeJ females were bred to keep that strain pure." In our experiments, more females and males were mated and 10–20 times more pups were obtained in each group. Thus, it is clear that my investigation and that of Brake and Evenson's are quite different and should not be compared.

B.M.C., L.V.G., A.M. and V.M. Ermakova refers to the comparison by the ACNFP of her research with that of Brake and Evenson[13] as "funny" because the latter investigators focused solely on reproductive physiology and did not feed rats before mating. But she overlooks the fact that her study can be viewed as a subset of the Brake and Evenson study because these authors measured mortality and growth in addition to numerous other parameters; it should be noted that the Brake and Evenson study conforms to internationally accepted norms for animal studies. In stark contrast to Ermakova's observations, they observed not a single mortality in four generations of pups fed GM soybeans at 14% of their dietary intake! Ermakova correctly notes that there is a difference in the timing of the exposure to soybeans in the feed of the dams (2 weeks prior and during, as opposed to only during, pregnancy). The assertion that Brake and Evenson missed the mutagenic effect of GM soy to the germ cells of the parents *per se* because they did not feed for 2 weeks prior to mating ignores the fact that there is no evidence that DNA is mutagenic; indeed, years of study suggest it is not[21,22]. Finally, Ermakova is somewhat disingenuous in claiming Brake and Evenson used a small number of animals because fewer animals were used in each of the five repetitions she reports. Brake and Evenson began with 16 animals (10 female, 6 male) in each group and then analyzed three offspring at 8, 16, 26, 32, 63 and 87 days of age for a total of 18 animals in each group. The numbers are therefore roughly comparable. Perhaps the biggest difference between the two studies is that Brake and Evenson used soybeans of known identity that were specifically grown under their control for the study, and they report a complete compositional analysis of the diets. Additionally, analysis of changes in the reproductive system parameters measured by Brake and Evenson are generally far more sensitive at revealing potential toxic effects than the weight gain and mortality observations of Ermakova. That notwithstanding, they report no pup mortality or other adverse effects over four generations of feeding RR soybeans.

Why have you so far forgone publishing your work in a peer-reviewed journal?

I.E. I first presented the data at the 11th Russian Gastroenterological Week (in a section on Nutrition and GMOs organized by the Moscow-based National Association for Genetic Safety) at the Russian Academy of State Service in Moscow, October 10–12, 2005. I was perplexed by my data and I appealed to scientists at this conference to repeat my experiments. This drew the attention of a journalist, Dmitry Starostin, and a note was published by the Russian federal news agency Regnum[23]. In December 2005, I spoke at a conference, "Epigenetics, Transgenic Plants and Risk Assessment", in Frankfurt am Main,

Germany. The paper detailing my preliminary results was published in the Proceedings of this conference[1]. Several papers have subsequently been published in different journals and proceedings. I have submitted a paper to a Russian peer-reviewed journal and am currently preparing other papers for consideration by peer-reviewed scientific journals in English.

B.M.C., L.V.G., A.M. and V.M. Ermakova does not answer the question. She has widely publicized her work at various congresses, meetings, press conferences and on the internet—this is not necessarily uncommon for major new findings. She strays, however, by announcing striking definitive conclusions from her experiments while at the same time claiming to entertain doubts in her own mind about her results. Her results depart so dramatically from previously reported findings as to be remarkable, and remarkable results demand remarkable support that Ermakova fails to provide.

We would add that even publication in a peer-reviewed journal does not *per se* validate scientific claims. It is up to the scientific community to weigh all reports against the best currently available evidence, including prior literature. Science needs to be repeated and to stand the test of time. When scientists circumvent peer review, they not only undermine science, they also undercut the credibility of science in the eyes of the general public[24]. If she had questions about her own results, as she says she did, she should not have devoted so much time to publicizing what are demonstrably flawed studies.

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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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.

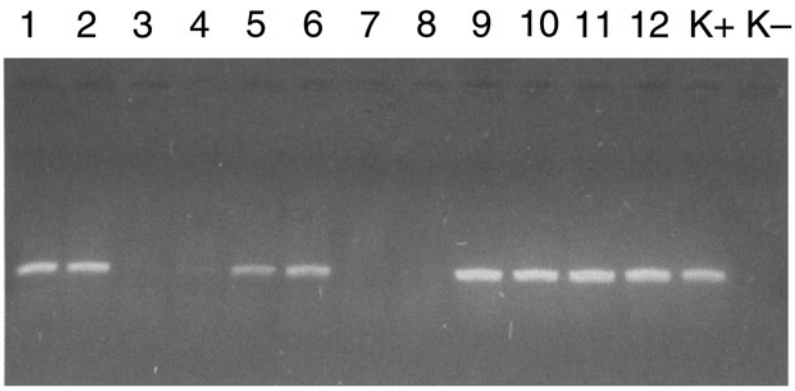

Figure 1 The 'blind' analysis of GM-soy and non-GM-soy samples using PCR. Lanes 1 and 2, GM-soy (flour); lanes 3 and 4, traditional soy flour; lanes 5 and 6, GM soy protein flour; lanes 7 and 8, traditional soy seeds; lanes 9 and 10, GM soy seeds after temperature treatment (t_o); lanes 11 and 12, GM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

GM-Free Cymru, Trefelin, Cilgwyn, Newport, Pembrokeshire, SA42 0QN, UK.

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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.

Carlo Leifert

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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.

Jack A Heinemann[1] & Terje Traavik[2]

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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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