Food and Chemical Toxicology 69 (2014) 357–359

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

# Conclusiveness of toxicity data and double standards

We would like to comment on your answers (Hayes, 2014a) concerning the retraction of our study (Seralini et al., 2012, Hayes, 2014b) by *Food and Chemical Toxicology* (FCT). Our study investigated the long-term effects in rats of consumption of two Monsanto products, a genetically modified (GM) maize and its associated pesticide, Roundup, together and separately. The decision to retract the paper was reached a few months after the appointment of a former Monsanto employee as "editor for biotechnology", a position created for him at FCT (Robinson and Latham, 2013). In a recent editorial, Portier and colleagues express concern about the "*dangerous erosion of the underpinnings of the peer-review process*" in the case of our study (Portier et al., 2014).

The criticisms from Monsanto and others focused on two aspects of our study: the relatively low number of rats used compared with the 50 per sex per group usual for carcinogenicity studies (OECD, 2009a) and the strain of rat used, the Sprague–Dawley. The critics alleged that the Sprague–Dawley rat was prone to tumours and that therefore the increased rate of tumorigenesis found in some of our treatment groups was purely random, even if this strain is commonly used in toxicology. Other answers to critics have been already published (Seralini et al., 2013).

These criticisms were subsequently adopted in your statement explaining the decision to retract our study. You wrote that the low number of rats and the strain selected meant that the conclusions on two aspects of our study – mortality and tumorigenesis – were "inconclusive" (Hayes, 2014a). In addition, you attested that our raw data were *"not incorrect"*, "*there was no misconduct"*, and that "*Unequivocally, the Editor-in-Chief found no evidence of fraud or intentional misrepresentation of the data"* (Seralini et al., 2014).

We are sceptical about the rationale given to retract our paper, in light of FCT's recent publication of another study (Zhang et al., 2014) which, like ours, investigated the potential chronic effects of consumption of a genetically modified (GM) crop. Unlike our study, however, it concluded that the GM crop tested, a transgenic insecticide-producing rice, was as safe and nutritious as conventional rice. Yet according to your criteria, it is at least as inconclusive as our study. Thus, it should not be published. Double standards are clearly used in evaluating Seralini et al. (2012), Hayes (2014b) and Zhang et al. (2014) in FCT.

Zhang et al. (2014) reached their conclusion of safety on the basis of only one treated group fed with the GMO, which they compared with two control groups, which can also bias the conclusion. Though 30 Sprague–Dawley rats were used per group, only 10 were measured for serum biochemistry, the same number as in our study.

In contrast with our study, Zhang and colleagues performed anatomopathology on an interim group of 10 rats analyzed at 52 weeks, though the results are not detailed in the paper. Zhang and colleagues also measured the mortality and tumour incidence of the remaining rats at the end of the experiment. This omits the chronological data provided in our experiment, in which the differential development of tumours in the treatment groups was traced through bi-weekly recording.

The criticism of the relatively low number of rats used in our experiment relies entirely on the misconception that it is a carcinogenicity study. It was not the case, as we stated clearly in the title and introduction. It was a long-term (chronic) toxicity study, which unexpectedly found increased rates of tumorigenesis and mortality in some treatment groups that we had to report.

The protocol set by the Organisation for Economic Cooperation and Development (OECD) for carcinogenicity studies on chemicals requires at least 50 animals per sex per group (OECD, 2009a). This large number of rats is intended to increase the "sensitivity" of the study (OECD, 2012), thereby protecting from false negative error, in which a carcinogenic effect exists but is missed because the number of rats used is too low to be representative of a population, or from false positive errors. Another reason for the large number of rats is that the background rate of so-called "spontaneous" tumours in laboratory rodents requires the use of large groups in order to reach statistical significance. The high background of tumors in historical data has not yet been proven as spontaneous, since the regulatory feed throughout the world may be contaminated with levels of GMOs and pesticides by contrast to our controls. Only the comparisons to the internal control are relevant. External controls, often called historical data, are irrelevant because the rats were raised in different conditions and may be subject to different feed contaminations even between different batches of the same brand of feed.

The number of rats we used was appropriate for a chronic toxicity study, as confirmed by the OECD chronic toxicity protocol, which specifies 20 animals per sex per group but only requires that 50% – 10 per sex per group – be analyzed for blood and clinical chemistry. This is also the same number that Zhang and colleagues analyzed. Thus regarding the number of rats, our study was equivalent to that of Zhang and colleagues and consistent with the analytical requirements of the OECD. In addition, the OECD chronic toxicity protocol 452 specifies that any "lesions" (the definition would include tumours) must be recorded (OECD, 2009b). This exactly reflects our practice.

In fact you clarified your position in a statement published in FCT: "To be very clear, it is the entire paper, with the claim that there is definitive link between GMO and cancer that is being retracted" (Hayes, 2014a). Yet we made no such "claim" in our

☆ DOI of original article: http://dx.doi.org/10.1016/j.fct.2012.08.005

http://dx.doi.org/10.1016/j.fct.2014.04.018

paper. We drew no inference and made no claims about "cancer" ; nowhere did we claim a "definitive link between GMO and cancer". In fact, our entire paper does not even mention the word "cancer". It should be noted that tumorigenesis is not synonymous with cancer. Tumours can be in some cases more rapidly lethal than cancers because their size can cause hemorrhages and possible impairments of vital organs, as well as secretion of toxins.

Your statement indicates that the retraction is based on confusion and over-generalization. The confusion, as indicated above, lies in the failure to understand that our study is about "long-term toxicity", not "cancer". Not surprisingly therefore, our study does not follow a carcinogenicity experimental protocol, which should be performed after a broadly focused long-term toxicity study such as ours.

Moreover, the stated reason for the retraction, the "inconclusive" nature of the tumours and mortality findings (Hayes, 2014a), does not equate to "error". Lack of conclusiveness and error are not synonymous.

Concerning over-generalization, contrary to your claim, the "entire paper" is not focused on the issue of tumours. The main part of the paper presents measurements of numerous biological parameters pertaining to the function of multiple organ systems, the statistical analysis and significance of which have not been challenged. Even if our paper had not mentioned the early appearance of tumours and premature deaths in rats, the chronic toxicity findings alone would justify its presence in the scientific record. These include effects on the disturbances of sex hormones and severe dysfunctions in liver and kidneys. Moreover, our study represents the only study on Roundup that includes blood analyses of treated animals (and from very low environmental levels, 0.1 ppb), since regulatory agencies only have chronic data with glyphosate used alone (Mortureux, 2013), which is highly less toxic than Roundup (Mesnage et al., 2013; Richard et al., 2005). Such analyses have never been conducted on the complete herbicide formulation for regulatory purposes.

A second rat feeding study with a GM crop, also published in FCT (Hammond et al., 2004) and also not retracted, also raises questions about double standards. This was a 90-day subchronic rat feeding study by Monsanto authors, examining the same GM maize that we tested over a chronic two-year period. In spite of the short duration, the Monsanto study still found differences in multiple organ functions between the GM and non-GM feeding groups. However, the authors dismissed them as not "*biologically meaningful*".

We have obtained the raw data of this study through a court case and re-analyzed the Monsanto data. We found potential signs of liver and kidney toxicity in rats fed NK603 maize (Spiroux de Vendômois et al., 2009). Our later study (Seralini et al., 2012, Hayes, 2014b) was designed to mirror the Monsanto study design and find out whether these initial signs of toxicity were really biologically irrelevant, as the Monsanto authors claimed, or escalated into serious pathology. We found that the latter was the case.

We conclude from this series of events that Hammond et al. (2004) was "inconclusive", in that changes were noticed in the GM feeding groups, but their significance was unclear because of the short subchronic study duration. Our study was the first and only attempt to clarify these inconclusive findings by extending the study length. Other researchers, including those working for Monsanto, are invited in turn to clarify the less "conclusive" aspects or our research: for example, by performing a large-scale carcinogenicity study.

A recent review (Meyer and Hilbeck, 2013) comparing our study with Hammond et al. (2004) and EFSA release of Monsanto's data on the same GM maize confirms our view that double standards were applied to reject our study alone. In this case, the body found to apply the double standard was not the editor of a journal but the European Food Safety Authority (EFSA).

Meyer and Hilbeck applied the same criteria used by EFSA to reject our study to the Monsanto conclusions, which were used to support regulatory authorization. They found that all three studies satisfied or failed to satisfy EFSA's criteria to a comparable extent, but that only our study was rejected by EFSA. In fact, EFSA did not even apply its criteria to Monsanto's studies. The authors also found that EFSA's criteria did not reflect standard practice in 21 other rat feeding studies of 12 months duration or longer, none of which have been retracted.

FCT's retraction of our paper, while not retracting studies – Zhang et al. (2014) and Hammond et al. (2004) – is an example of unscientific double standards. The decision to retract our paper appears to be results-driven, in that findings of safety in Zhang et al. (2014) and Hammond et al. (2004) have not been subjected to critical analysis and have been allowed to stand, whereas our findings of risk have been viewed with suspicion and forcibly retracted. As a result, economic interests have been given precedence over public health.

The use of double standards by the editors of scientific journals in evaluating studies on matters important to public health will damage the image and the value of science.

## Conflict of Interest

The authors declare that there are no conflicts of interest.

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Available online 18 April 2014