TESTBIOTECH Background 7 - 11 - 2014

Comments regarding the GRACE publication „Ninety-day oral toxicity studies on two genetically modified maize MON810 varieties in Wistar Han RCC rats (EU 7th Framework Programme project GRACE)“

Testbiotech e. V.
Institute for Independent Impact Assessment in Biotechnology

Andreas Bauer-Panskus & Christoph Then[1]

Summary

The results of a 90-day feeding study with genetically engineered maize MON810 that was part of the EU research project GRACE were published in October 2014. The results of this project are expected to have a significant impact on future standards in risk assessment of genetically engineered plants in the EU. The authors conclude that the diet did not trigger any toxicologically relevant effects in the rats.

However, this conclusion is not based on a sufficiently thorough assessment of the data that was obtained. In particular, it is unacceptable to dismiss the decrease in the total serum protein concentration and pancreas weight and the increase in blood glucose levels as toxicologically irrelevant. In terms of determining a dose with no toxic effects (no-effect level) the study by Zeljenková et al. (2014) must be considered invalid.

In addition, there are serious doubts about the scientific integrity regarding the entire publication process. It appears to be based on close affiliations between the corresponding author and the specialist journal, *Archives of Toxicology* and its editors. There is a long history of collaboration between the journal and industry, and a clear lack of declaration of conflicts of interest.

Given the importance of this study, the retraction of the paper is recommended. Re-publication should only be considered under a rigorous peer review process, and in a journal that is not influenced by any affiliations to the authors, and demonstrably has a history of the highest standards and integrity regarding conflicts of interest.

[1] Additional external expertise was made available by a toxicologist with long-term experience in regulatory toxicology.

1. Introduction

GRACE (**G**MO[2] **R**isk **A**ssessment and **C**ommunication of **E**vidence) is a publicly funded EU research project. The costs of the project add up to more than 7.7 million Euros, of which almost 6 million will come from the EU[3]. According to statements from the EU Commission, results from the GRACE project will have a significant impact on future methods and criteria that will be used in the EU to assess the risks of genetically engineered plants for cultivation or use in feed and food.

As a previous report from Testbiotech (Bauer-Panskus & Then, 2013) showed, about half of the experts participating in GRACE have close connections with organisations funded entirely or partly by the biotech industry. Amongst these organisations are the International Life Sciences Institute (ILSI) and the International Society for Biosafety Research (ISBR).

As part of the GRACE research project, a feeding study was conducted with genetically engineered maize MON810, which produces an insecticidal toxin. The rats used in the study were fed over a period of 90 days and the study was repeated once to minimise coincidental findings. The results were first presented at a stakeholder meeting in June 2014 and were commented on by Testbiotech at the time. However, there was no response to these comments and the final publication appeared in October 2014 (Zeljenková et al., 2014).

2. The results of the feeding study

The GLP[4]-controlled 90-day feeding study in Han Wistar RCC rats aimed at providing a safety evaluation of two varieties of MON810 as a dietary admixture of 11% (low dose) or 33% (high dose). The authors claim to have followed "the guidance for such studies published by the EFSA Scientific Committee in 2011 and the OECD Test Guideline 408.[5]" Although this is generally true, it needs to be stated that it is not entirely true, because the histopathological assessment[6] of macroscopic findings (in the low dose group) as required in Test Guideline 408 was obviously not followed.

The authors conclude that "the MON810 maize at a level of up to 33 % in the diet does not lead to toxicologically relevant effects in male and female Wistar Han RCC rats after 90-days of exposure." In particular, they dismiss the toxicological relevance of the observed significantly lower levels of total protein serum (TP). The authors argue that because "the magnitude of the differences between the groups was small … the effects are not considered to be related to the feeding of the GMO-containing diets." But TP was significantly and dose dependently decreased in male rats of feeding trial A and in females of feeding trial B. Although dose-dependent, the decrease in females of Trial B was statistically significant only at a

[2] GMO: genetically modified organisms; in this background paper the wording genetically engineered organism is used as equivalent.
[3] http://www.grace-fp7.eu/
[4] Good Laboratory Practice defines standards for the technical quality of toxicological studies
[5] This Guidance defines standards such as the size of the groups of animals used in the trials
[6] Microscopic assessment of animal tissue

concentration with 33 % genetically engineered maize. This however, was due to the rather high variability (coefficient of variation of 13.6%). In other words, individual animals with particularly low values rendered the 10.7% decrease in the female group with a concentration of 11% genetically engineered maize of trial B "insignificant", thereby masking a number of animals that were strongly affected. It is already arguable whether a more than 10% difference in group means in total serum protein can be considered "small". But more importantly, a total of 12 MON810-treated animals had values 20% lower than their respective control group mean (see Table 1 below).

Table 1: Individual animal data of total protein in serum of animals with values 20% lower than their respective control group means. Values in bold mark a 37% decrease compared to control group mean

Males of Trial A (Group mean: 61. 49 g/L)		**Females of Trial B** (Group mean: 70.24 g/L)			
33% GMO		11% GMO		33% GMO	
Animal No.	Value	Animal No.	Value	Animal No.	Value
1	45.6	297	54.4	282	53.6
6	48.8	299	53.2	283	**44.5**
-	-	302	56.2	285	55.4
-	-	303	52,4	286	47.7
-	-	304	**44.3**	288	54.6

As can be seen, there are animals with TP values up to 37% lower than the control group mean. Unfortunately, no urine samples were collected in these trials. Therefore, it is impossible to discern whether the low TP values were caused by an impairment of the synthetic capacity of the liver or by protein leakage into the urine.

It is surprising, that Zeljenková et al. (2014) do not even mention the paper by Hammond et al. (2006) which was later re-assessed by Spiroux de Vendomois et al. (2009). This study had a similar design assessing the effects of 11% and 33% MON 810, but in Sprague Dawley rats. In that study a statistically significant (10%) decrease in the albumin/globulin ratio was observed in males fed 33% MON 810 for 90 days, hinting at changes in the serum protein homeostasis.

A decrease in serum protein can have various reasons, most prominently the nephrotic syndrome[7] (Hodson et al. 2007) or an impaired protein synthesis of the liver (Majumdar et al. 1967). In addition, chronic inflammation as related to carcinogenesis has been mentioned (Ohki et al. 2012). In case of the nephrotic syndrome, proteins leak from the glomeruli of the kidney into the urine associated with hypoproteinaemia[8] and general oedema. From the paper by Zeljenková et al. (2014) it remains unclear whether generalised oedema were not present, forgotten to report or not noticed. In any event, nothing is mentioned in the histopathological part of the publication.

[7] Disturbance of urine excretion in kidney characterized by an increased permeability of the glomerulus
[8] Too low concentration of protein in the blood

Palanisamy et al. (2008) who induced renal damage in Wistar rats using a high-fructose diet observed an average plasma protein concentration of 4.75 g/100 ml in these animals (6.09 g/100 ml in their control group). This is an additional indication that the levels of total protein documented in the table above are to be considered pathological. Therefore, the dismissal of the decrease of the total serum protein concentration by Zeljenková et al. (2014) as toxicologically irrelevant is inacceptable. A re-assessment of the histological slides of these 12 animals should be performed and possibly additional investigations considered.

The second inappropriate dismissal involves weight changes of the pancreas and blood glucose levels. It is remarkable that the authors did not discuss these changes in conjunction, in spite of the well-known role of the pancreas in the regulation of blood glucose levels. Instead the discussion remains completely mute about the statistically significant and dose dependent decrease of the relative pancreas weight and dismisses the significant increase in blood glucose, because it was seen only in males of Trial A. A closer look however (Table 2), reveals that

- the pancreas weight was not only decreased in males of Trial A, but also in males of Trial B, although not statistically significant;
- there could be a threshold for the increase in Glucose levels as related to the decrease in relative pancreas weight. Whereas in the groups with a 10% weight decrease glucose levels were unchanged, the groups with a decrease in pancreas weight of about 20% had a 28% increase in blood glucose levels.

Table 2. Relative pancreas weight (Trial A and B) an glucose levels (Trial A) of male rats

Group	Trial A				Trial B	
	Rel. Pancreas weight (% of body weight)		Blood glucose (mmol/L)		Rel. Pancreas weight (% of body weight)	
		% change#		% change		% change
Control	0.141		8.47		0.141	
11% GMO	0.115*	-18	10.80	+28	0.129	-9
33% GMO	0.112*	-21	10.83	+28	0.126	-11

relative to control

*significantly different from control ($p<0.05$)

In addition, a scatter plot of all male animals of Trial A is suggestive of a negative correlation between relative pancreas weight and blood glucose levels (Figure 1)

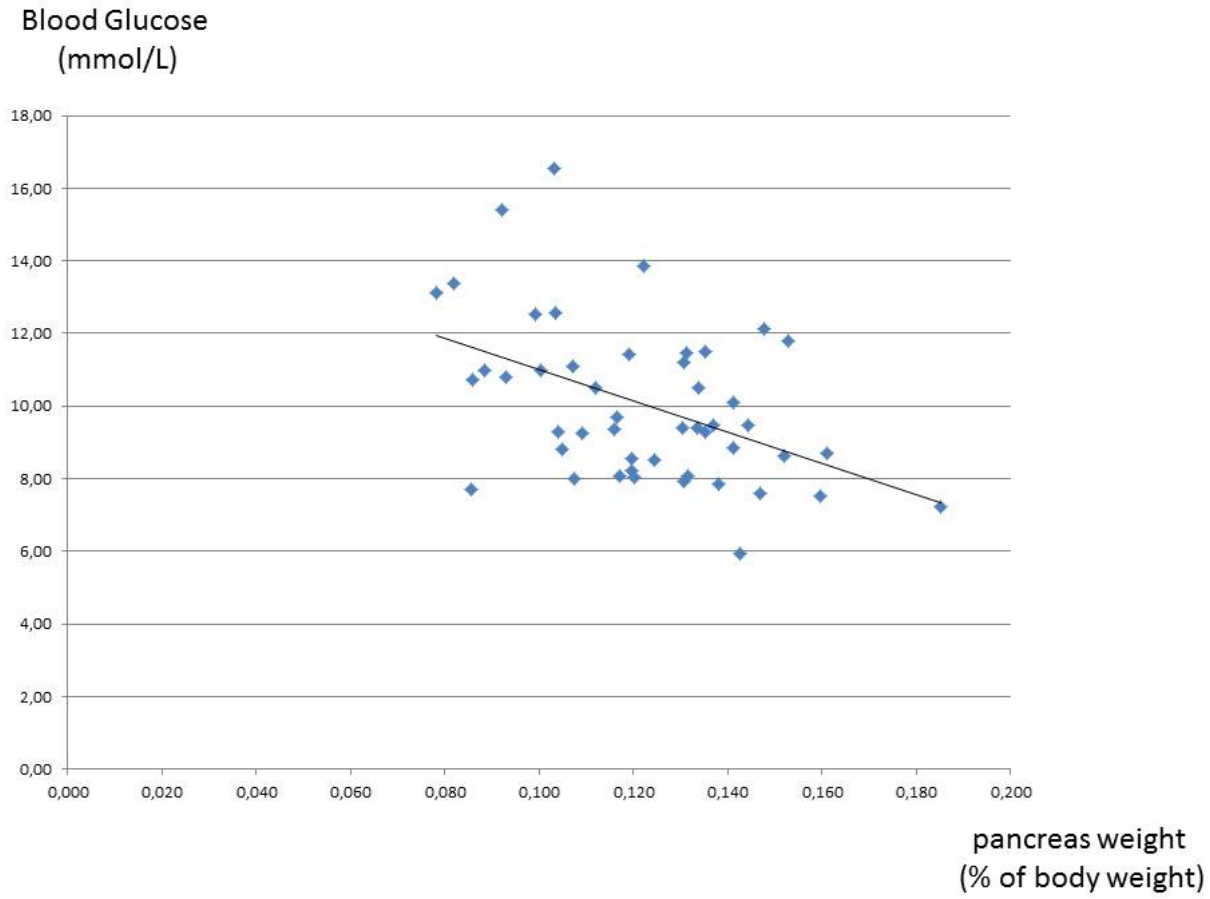

Figure 1: Scatter plot of blood glucose values versus relative pancreas weight of all males of Trial A.

In summary, these findings warrant a re-evaluation of the histological slides of these animals and, if possible a more thorough assessment using more specific staining and hematoxylin-eosin. From the data presented in the publication, the dismissal of the changes in pancreas weight and blood glucose concentration is not justified.

The fact that dose-dependent changes of total protein in serum, blood glucose levels and pancreas weight were seen in the MON 810-treated groups leads to the conclusion that the no-observed-effect level (NOEL)[9] is below a concentration of 11% genetically engineered maize in the diet. In other words the study conducted by Zeljenková et al. (2014) was unable to determine a NOEL and therefore, is invalid from the perspective of a toxicological safety assessment.

[9] A dose without treatment-related changes as compared to the control group,

3. Conflict of interests

The publication acknowledges two authors with a conflict of interest. First, according to the paper, Kerstin Schmidt *„provides consulting services in the field of biostatistics and has advised National and European Authorities, biotech and pharmaceutical companies as well as research institutions, also in the context of GMO risk assessment*.“ Second, Pablo Steinberg acknowledges membership in the Scientific Board of the Institut Danone Ernährung für Gesundheit e.V., funded by food company Danone. However, the declarations of interests are far from complete.

It appears that no explicit statements were requested from the authors to say that they had **no** conflicts of interest (e.g. with Monsanto) in addition to the general declaration of existing conflicts. In fact, such statements should be required at the planning phase of studies funded by public money, and the scientists participating in such studies should be selected accordingly.

Financial interests

For example, the declaration of interest of Kerstin Schmidt should be more precise. In fact, her company BioMath conducts contract research for Monsanto's monitoring programme for cultivation of maize MON 810 in Europe.[10] As the GRACE study was conducted with maize MON 810 from Monsanto, this surely should have been declared in the conflicts of interest statement. Further, Jörg Schmidtke is an employee of Kerstin Schmidt's company Biomath, so the connection to Monsanto's monitoring programme for maize MON 810 should also have been stated.

Non-financial interests

According to the journal's website, also *„interests that go beyond financial interests and compensation (non-financial interests) that may be important should be disclosed.“*[11] However, several authors of the GRACE paper did not reveal their interests in industry affiliated groups such as the International Life Sciences Institute (ILSI) or the International Society for Biosafety Research (ISBR).

a) The International Life Sciences Institute (ILSI)

The International Life Sciences Institute (ILSI) is financed by food, pharmaceutical and agrochemical companies. For example, its European branch (ILSI Europe) lists following members and supporting companies:[12] BASF, Bayer CropScience, Cargill, Coca-Cola, Danone, Dow Europe, DuPont de Nemours, General Mills, Kellogg, Mars, McDonald’s, Merck Consumer Healthcare. Monsanto, Nestlé, PepsiCo International, Pfizer Consumer Healthcare.

Currently, a staff member of Monsanto is president of ILSI's most influential body, the Board of Trustees[13].

[10] http://www.biomath.de/.cm4all/iproc.php/download/20141016%20List%20of%20publications%20BioMath.pdf?cdp=a. http://ec.europa.eu/food/plant/gmo/reports_studies/docs/report_2012_mon_810/report_2012_mon_810_farmer_questionnaire_survey_en.pdf

[11] http://www.springer.com/biomed/pharmacology+%26+toxicology/journal/204?detailsPage=editorialBoard

[12] http://www.ilsi.org/Documents/ILSI_2013_Member_List.pdf

[13] http://www.ilsi.org/Pages/Leadership.aspx

The work of ILSI has been criticised for many years partly because of its close cooperation with the tobacco industry to which the WHO publicly objected.[14] Also, because a letter from EFSA to the European Parliament in 2012 states, that ILSI experts *"cannot be considered for the role of chair or vice-chair of any of EFSA's scientific groups, nor can [s/he] become a member of a single mandate Working Group in a scientific area for which [s/he] ha[s] current experience at ILSI."* [15] This statement concerns all relevant sectors of expertise such as biotechnology, pesticides, food additives.

As a Testbiotech report (Bauer-Panskus & Then, 2013) revealed earlier, several GRACE experts have current or past connections to ILSI. Whereas the ILSI connections of Gijs Kleter, Esther Kok, Jean-Michel Wal and Joachim Schiemann have already been addressed by Bauer-Panskus & Then (2013), the ILSI connections of Pablo Steinberg, from the Institute for Food Toxicology and Analytical Chemistry, College of Veterinary Medicine Hannover, were unknown until now.[16] Steinberg plays a key role in this publication: He was the expert to present the first results of the feeding study in June 2014[17], further he is the publication's corresponding author.

According to the ILSI website, Pablo Steinberg serves as member of the working group „Determination of the Effectiveness of Dietary Exposure Reduction Measures on Human Health" of the ILSI task force „Process-related Compounds and Natural Toxins".[18] The working group and task force consist of employees of food corporations such as Nestlé, Pepsico, Kellog, or Mars. Steinberg was also involved in the EU funded ILSI project "Food Safety In Europe: Risk Assessment of Chemicals in Food and Diet" (FOSIE)[19] and is co-author of two ILSI publications.[20] Testbiotech strongly contends that this affiliation should have been mentioned under the declaration of conflicts of interest. These interests must be considered much more relevant than the aforementioned affiliation with Danone.

b) International Society for Biosafety Research (ISBR)

The International Society for Biosafety Research (ISBR) has close ties to the biotech and agrochemical industry and other industry groups such as ILSI. The society even shares the same address with the ILSI Research Foundation situated in Washington DC.[21] The funding of ISBR is not disclosed, but the society's conferences are sponsored by biotech corporations like Monsanto, Bayer, Dow AgroSciences, DuPont and Syngenta as well as by the biotech industry's global umbrella association, CropLife International.[22] In

14 http://www.who.int/tobacco/media/en/ILSI.pdf
15 http://www.efsa.europa.eu/en/press/news/120516.htm
16 http://www.tiho-hannover.de/?id=1051
17 R http://www.grace-fp7.eu/sites/default/files/GRACE%20Stakeholder%20Workshop%20May%202014%20Final%20Announcement.pdf
18 http://www.ilsi.org/Europe/Pages/Process-related-Compounds-and-Natural-Toxins-Expert-Groups.aspx
19 http://www.ilsi.org/Europe/Documents/FOSIENews.pdf
20 Barlow, S. M., Greig, J.B., Bridges, J.W., Carere, A., Carpy, A.J. M., Galli, C.L., ... & Steinberg, P. (2002) Hazard identification by methods of animal-based toxicology. Food and Chemical Toxicology, 40(2): 145-191. http://www.sciencedirect.com/science/article/pii/S027869150100117X
Dybing, E., Doe, J., Groten, J., Kleiner, J., O'Brien, J., Renwick, A.G., ... & Younes, M. (2002) Hazard characterisation of chemicals in food and diet: dose response, mechanisms and extrapolation issues. Food and Chemical Toxicology, 40(2): 237-282. http://www.sciencedirect.com/science/article/pii/S0278691501001156
21 http://isbr.info/About_Us
22 http://isbr.info/ISBGMO13/Sponsors

addition, the ISBR's Board of Directors consists almost exclusively of scientists with industry or ILSI affiliations (table 3).[23]

Table 3: Examples of affiliations of members of ISBR's Board of Directors

Name	ISBR position	Affiliation
Morven A. McLean	President	„ILSI's lead for sustainable agriculture and nutrition security across the organization internationally“
Alan Gray	President-elect	Co-author of several ILSI publications[24]
Monica Garcia-Alonso	Secretary	„worked for Syngenta for 19 years“
Donald MacKenzie	Treasurer	DuPont / Pioneer
Karen Hokanson	Director	Consultant for the Donald Danforth Plant Science Center, a research center funded by Monsanto[25]
Alan Raybould	Director	Syngenta

At least two authors of the paper „Ninety-day oral toxicity studies on two genetically modified maize MON810 varieties in Wistar Han RCC rats (EU 7th Framework Programme project GRACE)“ are members of ISBR:

- Ralf Wilhelm,[26]
- Joachim Schiemann.[27]

Testbiotech strongly contends that these affiliations too should have been mentioned under the declaration of conflict of interest.

[23] http://isbr.info/Board_of_Directors

[24] Roberts, A., Devos, Y., Raybould, A., Bigelow, P., & Gray, A. (2013) Environmental risk assessment of GE plants under low-exposure conditions. Transgenic research, 23(6): 971-983. http://link.springer.com/article/10.1007/s11248-013-9762-z
Wolt, J.D., Keese, P., Raybould, A., Fitzpatrick, J.W., Burachik, M., Gray, A., ... & Wu, F. (2010) Problem formulation in the environmental risk assessment for genetically modified plants. Transgenic research, 19(3): 425-436. http://link.springer.com/article/10.1007/s11248-009-9321-9

[25] http://www.zoominfo.com/CachedPage/?archive_id=0&page_id=6913215340&page_url=//maize.danforthcenter.org/scientists-research/research-institutes/institute-for-international-crop-improvement/team&page_last_updated=2014-08-14T07:29:06&firstName=Karen&lastName=Hokanson

[26] http://www.jki.bund.de/no_cache/de/startseite/institute/sicherheit-gentechnik/personal/dr-wilhelm-ralf.html

[27] http://www.jki.bund.de/no_cache/de/startseite/institute/sicherheit-gentechnik/personal/prof-dr-schiemann-joachim.html

4. Comments regarding the journal Archives of Toxicology

The study of the effects of MON810 varieties in rats discussed here was published in the peer-reviewed journal *Archives of Toxicology*. However, the decision of the GRACE consortium to publish the article in this journal is highly questionable for several reasons:

1. There are close ties between the editors of this journal and the study's corresponding author;
2. *Archives of Toxicology* has a long history of working closely with the tobacco industry, several of the editors of Archives of Toxicology have current or past ties to the pharma or tobacco industry.

4.1. Close ties between the editors of this journal and the study's corresponding author

According to the website of *Archives of Toxicology*,[28] the journal is edited by Jan G. Hengstler (Editor-in-Chief) and Hermann M. Bolt (Deputy Editor in Chief), both from the Leibniz Research Centre for Working Environment and Human Factors in Dortmund. The GRACE publication's main author, Pablo Steinberg, is also listed as an editor of the *Archives of Toxicology*. Furthermore, several editors of the journal have close ties to Pablo Steinberg.

- **Jan G. Hengstler (Editor-in-chief):** Jan G. Hengstler published many studies with Pablo Steinberg. Both worked as scientists at the Institute of Toxicology, University of Mainz.[29] Further, Pablo Steinberg is a member of the advisory board of the Leibniz Research Centre for Working Environment and Human Factors, while Jan Hengstler is director of this institute;[30]
- **Patrick R. Diel:** Like Pablo Steinberg, Patrick R. Diel is a long time member of the Senate Commission on Food Safety (SKLM) of the German Research Foundation (DFG);[31]
- **Hansruedi Glatt:** Prof. Glatt is another former scientist from the Institute of Toxicology, University of Mainz. He published several articles with Pablo Steinberg;[32]
- **Franz Oesch:** Prof. Oesch is Professor emeritus at the Institute of Toxicology, University of Mainz. Pablo Steinberg worked at this institution for many years (1986 – about 1998). Oesch published dozens of studies together with Pablo Steinberg.[33]
- **Albrecht Seidel:** Albrecht Seidel is another former scientist from the Institute of Toxicology, University of Mainz. He published several articles together with Pablo Steinberg.[34]

Given these close connections between Steinberg as the corresponding author with the editors and in awareness of Steinberg´s role as an editor at the *Archives of Toxicology*, one could assume that this publication is a case of 'self-publishing', which lacks sufficient external control. Since the reviewers of the article were not made public, there is room for further speculation. It is known that previous articles

[28] http://www.springer.com/biomed/pharmacology+%26+toxicology/journal/204?detailsPage=editorialBoard
[29] http://scholar.google.de/scholar?q=autor%3AHengstler+autor%3ASteinberg&btnG=&hl=de&as_sdt=0%2C5
[30] http://www.ifado.de/profil/organisation/beirat/index.html
[31] http://www.dfg.de/en/dfg_profile/statutory_bodies/senate/food_safety/index.html
[32] http://scholar.google.de/scholar?as_q=&as_epq=&as_oq=&as_eq=&as_occt=any&as_sauthors=glatt+steinberg&as_publication=&as_ylo=&as_yhi=&hl=de&as_sdt=0%2C5&as_vis=1
[33] http://scholar.google.de/scholar?as_q=&as_epq=&as_oq=&as_eq=&as_occt=any&as_sauthors=oesch+steinberg&as_publication=&as_ylo=&as_yhi=&hl=de&as_sdt=0%2C5
[34] http://scholar.google.de/scholar?q=autor%3A%22albrecht+seidel%22+autor%3Asteinberg&btnG=&hl=de&as_sdt=0%2C5

published in the *Archives of Toxicology,* dealing with health effects of smoking, were peer reviewed by experts from tobacco industry (see below).

4.2. The Archives of Toxicology and its editors have a history of working closely with industry

Documents found in the database of previously internal documents of the tobacco industry[35] show that the former editor-in-chief of *Archives of Toxicology*, Prof. Hermann Bolt (now listed as deputy editor), provided the tobacco industry with early access to studies on smoking. There are many documents in the database showing that Prof. Bolt invited scientists from the German Philip Morris owned laboratory, INBIFO (Institut für biologische Forschung) in Cologne, or the Philip Morris Contract Research Center in Belgium, to review studies, including studies on the effects on health from smoking. For example, in 1985, Bolt asked the INBIFO scientist Dr. Walk to review the article „The effect of smoke generation and manipulation variables on the toxicity of mainstream and sidestream cigarette smoke to monolayer cultures of L-929 cells“.[36] There were numerous peer review requests made to tobacco scientists by Prof. Bolt in the 1980s and 1990s.[37]
By the means of peer review, the tobacco industry could directly influence whether „undesirable“ studies were published or not. The journal also published scientific articles authored by Philip Morris scientists like Dr. Walk.[38]

Until 2008, Hermann Bolt was Director of the Institute of Work Physiology, University of Dortmund (now Leibniz Research Centre for Working Environment and Human Factors). Apart from giving the tobacco industry the opportunity to influence science on smoking (see above), his institute conducted research for Philip Morris from 2001 to 2004 and received US-$ 230.000 for a study on the “Development and application of an in vitro system for detection and quantification of urothelial genotoxicity of tobacco smoke-specific constituents utilizing classical genotoxic endpoints and cDNA expression profiling“. Whereas the leading role of Prof. Bolt in this study is obscured on the institute's website, internal documents from the tobacco database clearly identify Bolt as the principal investigator of this project.[39]

According to Testbiotech analysis, the current editor in chief Jan G. Hengstler also has close affiliations with industry. Hengstler is a director at the Leibniz Research Centre for Working Environment and Human Factors. In 2012, he co-authored an industry-friendly review regarding Bisphenol A (BPA). The review came to the conclusion that „BPA exposure represents no noteworthy risk to the health of the human population, including newborns and babies.“[40] However, according to investigations by the Sentinel Journal, several of

35 http://legacy.library.ucsf.edu/

36 http://legacy.library.ucsf.edu/tid/kuv22e00

37 http://legacy.library.ucsf.edu/tid/csl39e00, http://legacy.library.ucsf.edu/tid/tub83e00, http://legacy.library.ucsf.edu/tid/hfc12e00, http://legacy.library.ucsf.edu/tid/bgb12e00, http://legacy.library.ucsf.edu/tid/fra12e00, http://legacy.library.ucsf.edu/tid/aci27e00, http://legacy.library.ucsf.edu/tid/erk27e00, http://legacy.library.ucsf.edu/tid/kni12e00, http://legacy.library.ucsf.edu/tid/oht02e00,

38 http://legacy.library.ucsf.edu/tid/thj73e00, http://legacy.library.ucsf.edu/tid/dqh02e00, http://legacy.library.ucsf.edu/tid/jks12e00, http://link.springer.com/article/10.1007/BF00293630

39 http://www.ifado.de/biomarkers/tabakrauch/index.html, http://legacy.library.ucsf.edu/tid/oyt30i00, http://legacy.library.ucsf.edu/tid/isf20i00

40 Hengstler, J.G., Foth, H., Gebel, T., Kramer, P.J., Lilienblum, W., Schweinfurth, H., ... & Gundert-Remy, U. (2011) Critical evaluation of key evidence on the human health hazards of exposure to bisphenol A. Critical reviews in toxicology, 41(4): 263-291. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3135059/

the scientists involved in the review were either industry consultants or have close ties to industry (for example, through funding).[41]

Hengstler also supported a controversial call to the EU Commission which aimed to stop stricter regulation of endocrine disrupting chemicals.[42] According to several reports, nearly all supporters of this call, which was heavily criticised by other scientists, have close ties to industry.[43] Hengstler is also a member of the European Steering Committee of the organisation *ebtc* (Evidence-based Toxicology Collaboration),[44] which is sponsored by the oil and chemical industry.[45]

There are other examples of industry affiliations of members of the editorial board of Archives of Toxicology such as Olavi Pelkonen, University of Oulu, advisor for Pfizer and Orion Pharma,[46], Peter J. Kramer, former scientist with Merck, Darmstadt,[47] and Bennard Van Ravenzwaay, Senior Vice President, BASF SE, Experimental Toxicology and Ecology.[48]

Especially relevant in this context are the affiliations with the tobacco-industry. It is known that mechanisms developed by the tobacco industry to use biased science systematically as a tool to influence political decision making, also are applied in other contexts such as climate change[49]. Since ILSI also has a history of collaboration with the tobacco industry, we do not consider these observations to be coincidental.

Since GRACE is publicly funded and its outcome possibly decisive for future EU standards in the risk assessment of genetically engineered plants, it is unacceptable that this study was published in the *Archives of Toxicology,* which has such a deep and obvious history of affiliations with industry in addition to distinctly weak standards in defining conflicts of interest as well as having such a close relationship between editors and the corresponding author.

---

41 http://www.jsonline.com/watchdog/120827289.html

42 Dietrich, D.R., Aulock, S.V., Marquardt, H., Blaauboer, B., Dekant, W., Kehrer, J., Hengstler, J., Collier, A., Gori, G.B., Pelkonen, O., Lang, F., Barile, F.A., Nijkamp, F.P., Stemmer, K., Li, A., Savolainen, K., Hayes, A.W., Gooderham, N., Harvey, A (2013) Scientifically unfounded precaution drives European Commission's recommendations on EDC regulation, while defying common sense, well-established science and risk assessment principles. Chemico-Biological Interactions, 2013.

43 http://www.environmentalhealthnews.org/ehs/news/2013/eu-conflict-list
Bergman, Å., Andersson, A.M., Becher, G., van den Berg, M., Blumberg, B., Bjerregaard, P., ... & Zoeller, R.T. (2013) Science and policy on endocrine disrupters must not be mixed: a reply to a "common sense" intervention by toxicology journal editors. Environmental Health, 12(1): 69. http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=23981468
Grandjean, P., & Ozonoff, D. (2013) Transparency and translation of science in a modern world. Environmental health, 12(1): 70. http://www.ehjournal.net/content/12/1/70#B11
Gore, A. C., Balthazart, J., Bikle, D., Carpenter, D.O., Crews, D., Czernichow, P., ... & Watson, C.S. (2013) Policy decisions on endocrine disruptors should be based on science across disciplines: a response to Dietrich et al. European Journal of Endocrinology, 169(6): E1-E4. http://www.eje-online.org/content/169/6/E1.full

44 http://www.ebto x.com/steering-committee/

45 http://www.ebtox.com/sponsors/

46 http://www.ema.europa.eu/docs/en_GB/document_library/contacts/opelkonen_DI.pdf

47 http://webcache.googleusercontent.com/search?q=cache:VN7RKBLlcUwJ:peter-juergen-kramer.de/toxikologie-und-sicherheitspharmakologie/persoenlicher-hintergrund/+&cd=2&hl=de&ct=clnk&gl=de,
http://onlinelibrary.wiley.com/doi/10.1002/nadc.20060540717/abstract

48 http://www.researchgate.net/profile/Bennard_Van_Ravenzwaay

49 Oreskes & Conway (2014) Die Macchivallis der Wissenschaft, Wiley-VCH

5. Conclusions

There are a number of reasons that put into question the results and the scientific standards of the publication “Ninety-day oral toxicity studies on two genetically modified maize MON810 varieties in Wistar Han RCC rats (EU 7th Framework Programme project GRACE)”.

- The decrease of the total serum protein concentration and pancreas weight and the increase in blood glucose levels cannot be considered toxicologically irrelevant. In terms of determining a dose with no toxic effects (no-observed-effect level) the study by Zeljenková et al. (2014) must be considered invalid.
- The conflicts of interest of several authors of the GRACE study are either not addressed at all or only partly.
- There are several long term relations between the study's corresponding author, Pablo Steinberg, and members of the editorial board of *Archives of Toxicology*. Furthermore, Pablo Steinberg is even a member of the journal's editorial board himself. Altogether, publishing the GRACE study in the journal *Archives of Toxicology* gives the strong impression of 'self-publishing' in the sense that there was a lack of external control.
- Whereas *Archives of Toxicology* is a renowned journal in the field of toxicology, analysis shows that the journal has to be regarded as highly biased towards industry. The current main editors, Jan Hengstler and Hermann Bolt, both from the Leibniz Research Centre for Working Environment and Human Factors, have current or past ties to industry. Hermann Bolt even conducted research financed by the tobacco industry, and the journal has a long history of involvement with the tobacco industry. Several other members (apart from the two main editors) of the editorial board of Archives of Toxicology also have strong industry affiliations.

In conclusion, there are serious doubts about the outcomes as presented in the paper “Ninety-day oral toxicity studies on two genetically modified maize MON810 varieties in Wistar Han RCC rats (EU 7th Framework Programme project GRACE)”. In fact, our conclusion based on the study data, is that even the low dose cannot be considered free from MON 810-related effects. In addition, there are serious doubts about the scientific integrity regarding the entire publication process.

Given the importance of this study, we recommend the retraction of the paper. Re-publication should only be considered under a rigorous peer review process and in a journal with a scientific reputation not tarnished by questionable cooperation with industry, and which is not impacted by any affiliations to the authors and has the highest standards regarding conflicts of interest.

References

Bauer-Panskus, A. & Then, C. (2013) (DIS-)GRACE: Risk assessment on the leash of biotech industry. Testbiotech background. http://www.testbiotech.org/en/node/785

Hammond, B.G.; Dudek, R.; Lemen, J.K.; Nemeth, M.A. (2006) Results of a 90-day safety assurance study with rats fed grain from corn borer-protected corn. Food and Chemical Toxicology, 44: 1092-1099.

Hodson, E.M.; Willis, N.S.; Craig, J.C. (2007) Corticosteroid therapy for nephritic syndrome in children. Cochrane Database of Systematic Reviews (1): CD001(CD001533), 1-78.

Majumdar, C.; Tsukada, K.; Lieberman, I. (1967) Liver protein synthesis after partial hepatectomy and acute stress. Journal of Biological Chemistry 25: 700-704.

Ohki, S.; Shibata, M.; Gonda, K.; Machida, T.; Shimura, T.; Nakamura, I.; Ohtake, T.; Koyama, Y.; Suzuki, S.; Ohto, H.; Takenoshita, S. (2012) Circulating myeloid-derived suppressor cells are increased and correlate to immune suppression, inflammation and hypoproteinemia in patients with cancer. Oncology Reports, 28: 453-458.

Palanisamy, N.; Viswanathan, P.; Anuradha, C.V. (2008) Effect of Genistein, a Soy Isoflavone, on Whole Body Insulin Sensitivity and Renal Damage Induced by a High-Fructose Diet. Renal Failure, 30: 645–654.

Spiroux de Vendômois, J.; Roullier, F.; Cellier, D. ; Seralini, G.-E. (2009) A comparison of the effects of three GM corn varieties on mammalian health. International Journal of Biological Sciences, 5: 706-726.

Zeljenková, D., Ambrušová, K., Bartušová, M., Kebis, A., Kovrižnych, J., Krivošíková, Z., Kuricová, M., Líšková, A., Rollerová, E., Spustová, V., Szabová, E., Tulinská, J., Wimmerová, S., Levkut, M., Révajová, V., Ševcˇíková, Z., Schmidt, K., Schmidtke, J., La Paz, J.- L., Corujo, M., Pla, M., Kleter, G.A., Kok, E.J., Sharbati, J., Hanisch, C., Einspanier, R., Adel-Patient, K., Wal, J.-M., Spök, A., Pöting, A., Kohl, C., Wilhelm, W., Schiemann, J., Steinberg, P. (2014) Ninety-day oral toxicity studies on two genetically modified maize MON810 varieties in Wistar Han RCC rats (EU 7th Framework Programme project GRACE), Arch Toxicol., DOI 10.1007/s00204-014-1374-8