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MONSANTO COMPANY

SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

vs.

MONSANTO COMPANY,

Defendant.

Case No. CGC-16-550128

EXHIBITS 46 THROUGH 47 TO THE DECLARATION OF SANDRA A. EDWARDS IN SUPPORT OF MONSANTO'S MOTIONS *IN LIMINE* NOS. 6-30

Trial Date: June 18, 2018
Time: 9:30 p.m.
Department: TBD

EXHIBIT 46

Food and Chemical Toxicology 53 (2013) 473–474

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Food and Chemical Toxicology

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Letter to the editor

To the attention of Wallace Hayes.

Dear Editor of Food and Chemical Toxicology,

The Société Française de Pathologie Toxicologique (SFPT, French Society of Toxicologic Pathology, toxpathfrance.org) is a non governmental/non profit organization formed by veterinarians, physicians, pharmacists and biologists specialized in veterinary and toxicologic pathology. Its aim is to promote knowledge in pathology, toxicology and laboratory animal sciences for safety studies of drugs, chemicals and food products, and the role of the pathologist in the study design and data interpretation. As such, the SFPT feels compelled to point out weaknesses in the paper by Séralini et al. (2012), the number and importance of which make the study reported very difficult to interpret scientifically. We are aware that more arguments can be found in other scientific disciplines.

Before concentrating on veterinary and pathology aspects, we wish to briefly comment on two points. Regarding the statement that "The authors declare that there are no conflicts of interest", we respectfully disagree: Pr Gilles-Eric Séralini being President of the Scientific Board of the CRIIGEN, and the CRIIGEN having been a "major support" of the study, it seems to us that this should have been disclosed. Regarding the English, several native-English speaking colleagues complained about the difficulty to read the text because of many gross errors in expression: we consider that the journal reviewers could have alerted the authors on this point.

In our opinion, the study as reported (Ethics, §2.1) demonstrate a critical failure in the ethical supervision. First, it is not clear that the protocol was reviewed by a Committee of Animal Ethics/Institutional Animal Care and Use Committee, a basic requirement in the industry to even allow the purchasing of laboratory animals. "Animal experiments were performed according to ethical guidelines..." is not the same than stating that the protocol and the procedures were approved by an Ethical Committee. This is especially important in view of the statement that 31 parameters were analyzed (Biochemical analyses, §2.4): the quantity of blood removed is not indicated, and this could have had an effect on the well being of the animals and on their sanitary status. Clear guidelines of limits on blood sampling are available in the literature (Diehl et al., 2001), but it is impossible to know if they were followed in the study. Then, the choice of a low number of animals per group, thereby not following published guidelines (OECD, 2008, 2009), can be criticized as the data generated cannot be analyzed according to the state of the art methods and animals will have been used for no purpose, thus not respecting the humane principle of reduction (Russell and Burch, 1959). Last but not least, we were shocked at reading the ethical rules followed for euthanasia ("25% body weight loss, tumors over 25% body weight..." leading to euthanasia; Anatomopathology, §2.5) and at looking at Fig. 3J–L: the size of the tumors, with skin erosions and ulcerations, having certainly an impact on movement, feeding and pain, is unacceptable under well-known guidelines (Workman et al. 1998). This should have led to a much earlier euthanasia with respect to ethical humane concerns and casts doubts about the "careful monitoring" (Anatomopathological observations, §3.2) of animals. No argument, apparently to leave tumors develop as much as possible, should have prevailed. Again this demonstrates a lack of understanding of animal physiology and ethics, and a lack of supervision by the Ethical Committee and by a site veterinarian ("vétérinaire sanitaire", a function mandatory under French law, see Article R203-1 5°). We are surprised that these major ethical issues were not clarified during the review that the paper underwent before approval for publication.

We lack a clear understanding of the procedure followed for the pathologic examination of tissues. Especially, we have no idea, given the authors' affiliations, of who performed this pathologic examination. Also, for toxicology and carcinogenicity studies like this one, there are best practices available for primary reading (Crissman et al. 2004) and for peer review (Morton et al., 2010). The errors due to the lack of use of internationally recognized nomenclature and diagnostic criteria (as can be seen in the use of the term nephroblastoma in legend from Table 2 being called Wilm's tumor in the text, and in its erroneous assessment as GMO-related while it is an embryonal tumor found in young rodents) could have been avoided by following those best practices. The SFPT has among its members scientists from the industry, academia and also independent consultants. It would be happy to supply names of renowned colleagues, French or foreign, with a track record of assessment of toxicology and carcinogenicity studies, who would have increased the quality of the pathological assessment and the overall value of this study.

We already hinted at deficiencies in the study design: from a statistical perspective, this long term study is largely underpowered with only 10 animals per sex per group, while the accepted guidelines (OECD, 2008, 2009) recommend using groups of at least 50 animals per sex per group, and define strict survival rate criteria that the groups must respect for the results to be considered valid. With mortality rates of 50 or 70% in some groups, we wonder whether these criteria were consistently met. As far as we understand, all results are based on descriptive analyses such as percentage calculation, but there was no thorough mortality analysis (how to compare 3/10 with 5/10?) nor tumor incidence and date of onset analysis with recognized statistical methods (Peto et al., 1980). Not taking into account the high variability (because of the small size

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of the groups) makes all reported incidences and further conclusions non-meaningful and leads the authors to a gross over interpretation of the pathology data.

We are puzzled by the inclusion of organ weights: in carcinogenesis studies, geriatric changes and, at later stages, the development of tumors confound the usefulness of organ weight data, which are therefore not recommended (OECD, 2008). We are also puzzled by the mention of 2 tumors beginning to "reach a large size ... up to 600 days earlier in 2male groups eating the GM maize": we understand that those 2 males are the ones affected early with the nephroblastomas mentioned above, and this confirms us in our analysis of the origin and absence of treatment-relationship of those tumors.

As the paper reports a *de facto* carcinogenesis study, we expected to see some of the classical objectives of such a study type: the identification of the carcinogenic properties of a chemical; the identification of target organs; the characterization of a dose–response relationship; the identification of a no-observed (adverse) effect level (NO(A)EL); the prediction of carcinogenic effects of a chemical at human exposure levels; understanding the mode of action for treatment-related findings. We do not find in the results and in the discussion all the information necessary to meet these objectives; especially the non-conventional data reporting, with only an extract of the study data, and the data presentation, with merging of various pathological entities in Table 2 and focus on non-relevant findings, prevent us to make a scientific evaluation of the objectives discussed above. A full incidence list of all tumors by type, sex and group would have been more useful than a full plate of photos.

We spotted other errors in the Anatomopathological observations (§3.2): presenting incomplete neoplastic and non-neoplastic findings; considering hepatic foci of altered cells as necrotic foci; hepatic congestion being not relevant if the rats were found dead or moribund; diagnosing macroscopic necrotic foci; presenting common neoplasms in treated animals as treatment-specific; not presenting historical data (particularly useful in this case given the small group size); noting a difference between photos1 and 2 in Fig. 4, and reporting the increase in smooth endoplasmic reticulum while this change should be regarded as adaptive to xenobiotic metabolism (in the absence of contrary evidence); not presenting a mechanism for the increase in glycogen noted on the EM photos (especially in the absence of fasting status of the animals at euthanasia); lacking to critically discuss the pituitary tumors and the mammary tumors (prolactin-dependent); lacking to critically discuss the chronic progressive nephropathy in old rats. This list is not exhaustive, but is enough to cast doubts about the value of all the anatomopathological results.

In conclusion, the SFPT is deeply convinced that a thorough evaluation of all products is necessary before marketing but also during the product life, in order to guarantee as much as possible human, animal and environment safety. However, given this study presents serious deficiencies in the protocol, the procedures and the interpretation of the results, the SFPT cannot support any of the scientific claims drawn by the authors, and any relevance for human risk assessment.

This letter presents the consensus scientific opinion of the Conseil d'Administration of the SFPT.

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Further reading

For all pathology data not substantiated by a reference, please refer to recent and comprehensive toxicologic pathology textbooks, such as Greaves, 2012. Histopathology of Preclinical Toxicity Studies: Interpretation and Relevance in Drug Safety Evaluation, fourth ed. Academic Press, New York.

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EXHIBIT 47

Food and Chemical Toxicology xxx (2012) xxx–xxx

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Food and Chemical Toxicology

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Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize

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ABSTRACT

The health effects of a Roundup-tolerant genetically modified maize (from 11% in the diet), cultivated with or without Roundup, and Roundup alone (from 0.1 ppb in water), were studied 2 years in rats. In females, all treated groups died 2–3 times more than controls, and more rapidly. This difference was visible in 3 male groups fed GMOs. All results were hormone and sex dependent, and the pathological profiles were comparable. Females developed large mammary tumors almost always more often than and before controls, the pituitary was the second most disabled organ; the sex hormonal balance was modified by GMO and Roundup treatments. In treated males, liver congestions and necrosis were 2.5–5.5 times higher. This pathology was confirmed by optic and transmission electron microscopy. Marked and severe kidney nephropathies were also generally 1.3–2.3 greater. Males presented 4 times more large palpable tumors than controls which occurred up to 600 days earlier. Biochemistry data confirmed very significant kidney chronic deficiencies; for all treatments and both sexes, 76% of the altered parameters were kidney related. These results can be explained by the non linear endocrine-disrupting effects of Roundup, but also by the overexpression of the transgene in the GMO and its metabolic consequences.

1. Introduction

There is an ongoing international debate as to the necessary length of mammalian toxicity studies in relation to the consumption of genetically modified (GM) plants including regular metabolic analyses (Séralini et al., 2011). Currently, no regulatory authority requests mandatory chronic animal feeding studies to be performed for edible GMOs and formulated pesticides. However, several studies consisting of 90 day rat feeding trials have been conducted by the biotech industry. These investigations mostly concern GM soy and maize that are rendered either herbicide tolerant (to Roundup (R) in 80% of cases), or engineered to produce a modified *Bt* toxin insecticide, or both. As a result these GM crops contain new pesticide residues for which new maximal residual levels (MRL) have been established in some countries.

If the petitioners conclude in general that there is no major change in genetically modified organism (GMO) subchronic toxicity studies (Domingo and Giné Bordonaba, 2011; Hammond et al., 2004, 2006a,b), significant disturbances have been found and may be interpreted differently (Séralini et al., 2009; Spiroux de Vendômois et al., 2010). Detailed analyses have revealed alterations in kidney and liver functions that may be the signs of early chronic diet intoxication, possibly explained at least in part by pesticide residues in the GM feed (Séralini et al., 2007; Spiroux de Vendômois et al., 2009). Indeed, it has been demonstrated that R concentrations in the range of 10^3 times below the MRL induced endocrine disturbances in human cells (Gasnier et al., 2009) and toxic effects thereafter (Benachour and Seralini, 2009), including *in vivo* (Romano et al., 2012). After several months of consumption of an R-tolerant soy, the liver and pancreas of mice were affected, as highlighted by disturbances in sub-nuclear structure (Malatesta et al., 2008a, 2002a,b). Furthermore, this toxic effect was reproduced by the application of R herbicide directly to hepatocytes in culture (Malatesta et al., 2008b).

Abbreviations: GM, genetically modified; R, Roundup; MRL, maximal residual levels; GMO, genetically modified organism; OECD, Organization for Economic Cooperation and Development; GT, glutamyl-transferase; PCA, principal component analysis; PLS, partial least-squares; OPLS, orthogonal partial least-squares; NIPALS, Nonlinear Iterative Partial Least Squares; OPLS-DA, Orthogonal Partial Least Squares Discriminant Analysis; G, glycogen; L, lipid droplet; N, nucleus; R, rough endoplasmic reticulum (on microscopy pictures only); U, urinary; UEx, excreted in urine during 24 h; APPT, Activated Partial Thromboplastin Time; MCV, Mean Corpuscular Volume; PT, Prothrombine Time; RBC, Red Blood Cells; ALT, alanine aminotransferase; MCHC, Mean Corpuscular Hemoglobin Concentration; A/G, Albumin/Globulin ratio; WBC, White Blood Cells; AST, aspartate aminotransferase.

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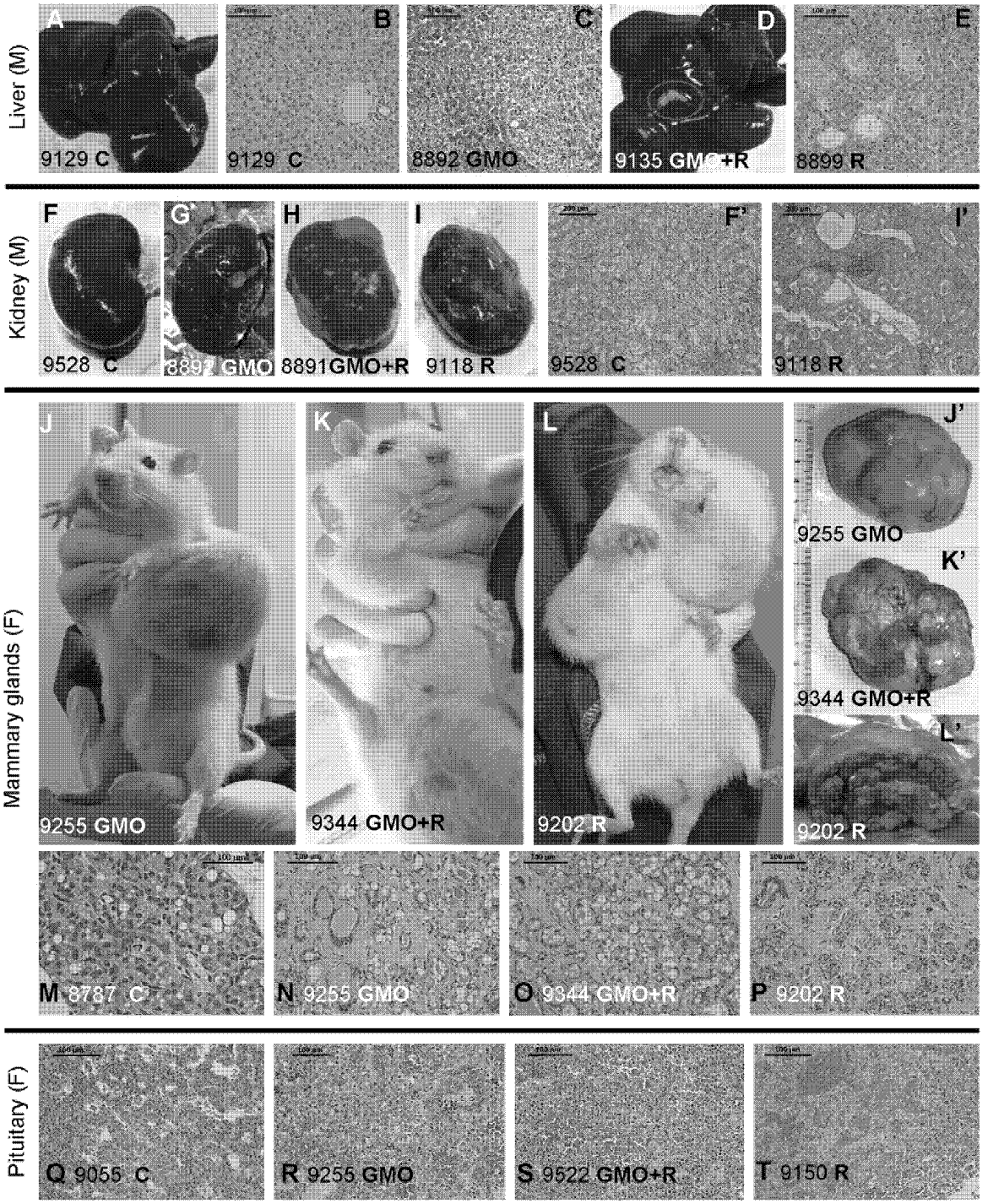

Fig. 3. Anatomopathological observations in rats fed GMO treated or not by Roundup, and effects of Roundup alone. Macroscopic and microscopic photographs show male livers (A–E) and left kidneys (F–I'), female mammary glands (J–P) and pituitaries (Q–T), according to Table 2. The number of each animal and its treatment is specified. Macroscopic pale spots (D) and microscopic necrotic foci in liver (C clear-cell focus, E basophilic focus with atypia), and marked or severe chronic progressive nephropathies, are illustrated. In females, mammary tumors (J,J',N adenocarcinoma and K,K',L,L',O,P fibroadenomas) and pituitary adenomas (R–T) are shown and compared to controls (C after the rat number).

In addition, cytochrome activities also generally increased in the presence of R (in drinking water or GM diet) according to the dose up to 5.7 times at the highest dose. Transmission electron microscopic observations of liver samples confirmed changes for all treated groups in relation to glycogen dispersion or appearance in lakes, increase of residual bodies and enlargement of cristae in mitochondria (Fig. 4). The GM maize fed groups either with or without R application (in plants) showed a reduced transcription in mRNA and rRNA because of higher heterochromatin content, and decreased nucleolar dense fibrillar components. In the GMO + R group (at the highest dose) the smooth endoplasmic reticulum was drastically increased and nucleoli decreased in size,

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