EXHIBIT 4

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MONSANTO TELEFAX TRANSMITTAL SHEET

TO	ALAN WILSON, DONNA FARMER & BILL HEYDENS
LOCATION	MONSANTO STL CC E2SE
FAX NUMBER	4028
FROM	MARK MARTENS
DATE	15/02/1999
SUBJECT	PROF PARRY'S REPORT
NR OF PAGES (incl this page)	12

Dear Alan, Donna and Bill,

Please find herewith Prof. Parry's evaluation of the 4 papers I sent him on genotoxicity of glyphosate and Roundup. Could you study this carefully and formulate comments. We will then have to set up a conference call with Larry (who also received this fax) to decide what to do next.

Best regards,

Mark.

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Dr Mark A Martens
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11 February 1999

Dear Dr Martens

You will find enclosed my evaluation of the four papers you provided concerning the potential genotoxicity of glyphosate and Roundup. Although each of the papers have weaknesses, I have avoided a report which attempts to focus upon these weaknesses. Rather, I have attempted to "pull out" the data which provide an aid to the understanding of the potential mechanisms of glyphosate genotoxicity and indicated how you might clarify these mechanisms. It has been my experience with Regulatory Agencies that a positive attitude to published data is a more productive approach than just criticising individual studies.

I assume that you will already have in house data for some of the suggested experiments. In my view the *in vitro* micronucleus work suggested would be the most productive way of clarifying the question of mechanisms. I would be happy to provide you with further suggestions as to detailed protocols for such studies. They would make a rather nice Ph.D project for a graduate student if you could find the funding.

I have enclosed my invoice for the evaluation.

Yours sincerely

Professor James M. Parry

Tel 01792 295361 Fax 01792 295447

Curriculum Vitae

James M. Parry,

B.Sc. Botany (London), Ph.D. Genetics (Liverpool), D.Sc. (Liverpool).

Date of Birth: 9.10.1940.

Professor of Genetics, School of Biological Sciences,

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Teaching Experience

General Genetics, Human Genetics, Molecular and Microbial Genetics, Basic Toxicology, Environmental and Aquatic Toxicology.

Research Interests

Mechanisms for maintaining the fidelity of the genome, role of environmental chemicals in the induction of genetic changes leading to the formation of birth defects and cancer. Mechanisms of action of chemicals leading to the disturbances in chromosome segregation and to chromosome aneuploidy. Mechanisms of formation of DNA lesions and base sequence changes *in* vitro and *in* vivo. Genetic effect of environmental chemicals upon aquatic species.

Research Laboratory is staffed by four senior research assistants, twelve graduate students and three technicians.

The Laboratory currently coordinates the European Union Research Project on the "Mechanisms of Chemically induced aneuploidy" and collaborates in the European Union Projects on "Neurotoxicity of Mercury Compounds" and "State of the art methods for detecting chemical carcinogens". The Laboratory also receives research support from the Medical Research Council, Health and Safety Executive, Ministry of Agriculture Food and Fisheries and a variety of Pharmaceutical and Chemical Companies. Author of over 200 scientific papers and articles.

Public Activities

President:	UK Environmental Mutagen Society 1974-1977
Vice-President:	European Environmental Mutagen Society 1993-1995.
President:	European Environmental Mutagen Society 1995-1997.
Editor:	the Scientific Journal "Mutagenesis"
Member:	Editorial Board "Mutation Research"
Member:	Advisory Board, Small Area Statistics Unit, St. Mary's Hospital London.
Member:	Advisory Board, Department of Health Toxicology Unit, Hammersmith Hospital, London.
Chairman:	Department of Health Advisory Committee on the Mutagenicity of Chemicals.
Member:	Department of Health Advisory Committee of the Carcinogeniety of Chemicals.
Member:	1994-1997 Working Party of Committee on Medical Aspects of Food on "Cancer and the Diet".
Member:	Medical and Toxicology Panel of UK Scientific Committee on Pesticides.
Member:	Ad-hoc Consultancy Group to Commission of European Communities Committee on "Plant Protection Products" (Pesticides).

These public duties particularly relate to my interests and expertise in the evaluation of the hazards and risks of environmental chemicals upon the human population and upon environmental species.

Evaluation of potential genotoxicity of Glyphosate and Round up Mixtures

Professor J. M. Parry, Centre for Molecular Genetics and Toxicology, School of Biological Sciences, University of Wales Swansea, Swansea SA2 8PP.

Individual Evaluation of Publications

Rank *et al* (1993)

Test Methods Used

Salmonella Assay TA98 and TA100

Roundup mixture tested - positive minus S9 in TA98, positive plus S9 in TA100.

Mouse Micronucleus Bone Marrow Assay - spontaneous frequency 0.3% i.e. 3 per 1000.

Roundup mixture - no effect up to 200mg/kg - only sampled at 48 hrs.

Glyphosate isopropylamine salt - no effect up to 200mg/kg, only 1 dose point gave reduction in PCE/NCE ratio - for other concentrations there was no evidence that compounds reached bone marrow.

Allium cepa Root Cytogenetics

Roundup mixture - positive response greater than 720µg/litre - characterised as spindle disturbance.

Glyphosate isopropylamine salt - no effect.

Conclusion

In vitro evidence of genotoxic effect for Roundup mixture, inadequate *in vivo* studies.

Bolognesi *et al* (1997)

Test Methods Used

Mouse Micronucleus Bone Marrow Assay - spontaneous frequency 0.075% i.e. 0.75 per 1000.

Roundup Mixture - positive response at 450mg/kg (multiple dosing).

Glyphosate - positive response at 300mg/kg (multiple dosing).

Reduction in PCE/NCE ratio - clear evidence that compounds reached the bone marrow.

Sister Chromatid Exchange in Human Lymphocytes *in vitro*

Roundup Mixture - positive response at 100μg/ml.

Glyphosate - positive response at 1000μg/ml.

DNA damage - alkaline elution in liver and kidney

Roundup Mixture - increase in single strand breaks in both liver and kidney at 4 hrs following 300mg/kg.

Glyphosate - increase in single strand breaks in both liver and kidney at 4 hrs following 300mg/kg.

Induction of 8-OHdG in liver and kidney as measure of oxidative damage

Roundup Mixture - increase in 8-OHdG in both liver and kidney.

Glyphosate - increase in 8-OHdG in liver only.

Note. Glyphosate induced a quantitatively greater increase in 8-OHdG in liver than Roundup mixture.

Conclusion

Positive response *in vitro* SCE for both compounds, response at 10 times lower concentration for Roundup mixture.

Both Glyphosate and Roundup mixture produced positive response in mouse bone marrow micronucleus assay.

Both Glyphosate and Roundup mixture produced increase in DNA strand breaks in mouse liver and kidney.

Glyphosphate increased 8-OHdG in mouse liver.

Roundup mixture increased 8-OHdG in mouse liver and kidney.

Peluso *et al* (1998)

Test Method Used

^{32}P post-labelling in mouse liver and kidneys.

Roundup Mixture - increase in uncharacterised DNA adducts in liver and kidney at concentrations of 400, 500 and 600mg/kg.

Glyphosate isopropylammonium salt - no increase in DNA adducts in liver and kidney at concentrations of 130 and 270mg/kg.

Note. No evidence of the sensitivity of the ^{32}P assay in the authors hands is provided in the paper.

Conclusion

Roundup Mixture produced increase in DNA adducts in mouse liver and kidney.

No increase produced by Glyphosate at concentrations calculated to roughly equate with concentrations in Roundup Mixture.

Loi *et al* (1998)

Test System Used

Induction of chromosome aberrations and SCE in bovine lymphocytes *in vitro*

Glyphosate - dose-dependent increase in chromatid aberrations 17 to 170μM solutions, dose-dependent decrease in mitotic index.

Glyphosate - increase in sister chromatid exchange 17 to 170μM solutions.

G6PD activity as measure of oxidative stress

Glyphosate - increase in G6PD activity following exposure to 17 to 170μM solutions.

Glyphosate + anti-oxidant N-acetyl-cysteine - increase in G6PD reduced in presence of anti-oxidant.

Note. Structure activity relationship between Glyphosate used and isopropylammonium salt

unclear.

Conclusion

Increase in chromatid aberrations of SCE following Glyphosate exposure.

Increase in G6PD activity following Glyphosate exposure.

Increase in G6PD reduced by presence of anti-oxidant.

Chemical preparations tested in the 4 papers

Glyphosate

Bolognesi *et al* (1997), Loi *et al* (1998)

Glyphosate isopropylammonium salt

Peluso *et al* (1998), Rank *et al* (1993)

Roundup Mixture

30.4% - Peluso *et al* (1998), Bolognesi *et al* (1997).

48% - Rank *et al* (1993)

Source of chemicals

Glyphosate - *Soc. It. Chem.* Rome - Bolognesi *et al* (1997), Peluso *et al* (1998).

Lab. Serv. Anal. Bologna - Loi *et al* (1998).

Dr. Ehrenstorfer - Rank *et al* (1993).

Roundup Mixture - Monsanto, Italy - Peluso *et al* (1998), Bolognesi *et al* (1997).

Monsanto, USA - Rank *et al* (1993).

Comparison of results obtained in the analysis of the effects of Glyphosate and Roundup Mixture

Concordant Results

Mouse Micronucleus Assay - Positive for both.

SCE *in vitro* human lymphocytes - Both positive, Roundup more potent.

DNA strand breaks - Positive with both.

Non-Concordant Results

Allium Cytogenetics - Positive only with Roundup Mixture.

8-OHdG - Roundup positive in kidney, non-significant increase in liver.
Glyphosate positive only in liver.

^{32}P-postlabelling - Roundup positive in liver and kidney.
Glyphosate negative.

Conclusions

Roundup mixture induced frameshift mutations in *Salmonella typhimurium* TA98 in the absence of S9 mix. Roundup mixture induce base substitution mutations in *Salmonella typhimurium* TA100 in the presence of S9 mix.

These data appear to be in marked contrast with other published studies (Shirasu *et al* 1982, Wildeman and Nazar 1982, Li and Long 1988.

***In vitro* Cytogenetics**

a) Glyphosate induces a dose-dependent increase in chromatid aberrations *in vitro* in bovine lymphocytes over a concentration range of 17 to 170μM solution.

b) Sister chromatid exchanges induced in human lymphocytes by both Glyphosate and Roundup mixture. Roundup mixture produced a positive result at lower concentrations.

c) In Allium root tips positive result produced by Roundup mixture, no response with Glyphosate. Predominant aberrations were indicative of spindle damage.

d) Measurements of the activity of G6PD suggests that Glyphosate increases activity indicating oxidative stress. This modification of G6PD activity was reduced in the presence of the anti-oxidant N-acetyl-cysteine.

***In vivo* Studies**

Both Glyphosate and Roundup mixture produced a positive result in the mouse bone marrow micronucleus assay (Bolognesi *et al* 1997). The positive results were in contrast with the negative results of Rank *et al* (1993). The positive study had a clear demonstration of bone marrow toxicity and involved multiple dosing (2 doses) with the test agents in contrast to a single dosing used by Rank *et al* (1993).

The data of Bolognesi *et al* (1997) indicate that Glyphosate is a probable *in vivo* genotoxin. However, the study of Bolognesi *et al* (1997) involved only 3 or 4 animals at each sampling time and dose point and cannot be considered to be of OECD guideline standard. The frequency of micronuclei in the control culture in the Bolognesi *et al* (1997) study was substantially lower than that of the Rank *et al* (1993) study.

Both Glyphosate and Roundup induced significant increases in DNA strand breaks in mouse liver and kidney. Roundup mixture increased 8-OHdG in mouse liver and kidney. Glyphosate increased 8-OHdG in mouse liver. These data indicate that Glyphosate produces oxidative damage *in vivo* which leads to single strand breaks and 8-OHdG lesions in exposed tissues. The unique positive result in mouse kidney with Roundup mixture suggests a synergistic effect of some component of the mixture.

The ^{32}P postlabelling study of Peluso *et al* (1998) indicates that Roundup is capable of inducing DNA adducts (uncharacterised) in mouse liver and kidney. Glyphosate alone,

at equivalent concentrations to that in Roundup, failed to increase adducts. These data provide some evidence to support the concept that any *in vivo* activity of Glyphosphate may be potentiated by other components of the Roundup mixture.

The overall data provided by the four publications provide evidence to support a model that Glyphosate is capable of producing genotoxicity both *in vivo* and *in vitro* by a mechanism based upon the production of oxidative damage. If confirmed, such a mechanism of genetic damage would be expected to be produced at high concentrations of the herbicide and would be relevant only when the anti-oxidant protective mechanisms of the cell are overwhelmed. Thus, I would conclude that if the mechanism of action can be proved to be based upon oxidative damage then hazard and risk assessment could be based upon a non-linear model with a threshold of activity at low doses.

Questions raised by the studies

1) Role of components of mixture which leads to high levels of activity of Roundup?

2) Is the genotoxic activity observed due to oxidative damage?

3) Can the genotoxic activity be reduced by anti-oxidants?

Recommendations for further work to clarify the potential genotoxic activity of Glyphosate

Bacteria

I recommend a repeat of Salmonella studies particularly with Roundup mixtures. I would be surprised if these data are not already available in-house.

Cytogenetics

I recommend an *in vitro* micronucleus study preferably in human lymphocytes. If combined with analyses of the micronuclei for the presence and absence of centromeric DNA this study would indicate whether Glyphosate induces predominantly chromosome structural

or numerical damage.

The *in vitro* micronucleus assay would allow both:-

a) The assessment of the potential influence of anti-oxidants upon the genotoxic potential of Glyphosate - Note the measurement of the effect of anti-oxidant as a genetic endpoint is a critical deficiency in the Loi *et al* (1998) study.

b) Assessment of the individual components of the Roundup Mixture to determine whether there is any component(s) which act synergistically to increase the potential genotoxicity of Glyphosate. Such studies could be designed to investigate a panel of mixtures leaving out one component of the mix for each individual experiment.

***In vivo* studies**

In view of the limitations of the Bolgnesi *et al* (1977) study i.e.

limited number of animals

single dose of compound

low spontaneous micronucleus frequency

it would be worth repeating the study to a more comprehensive design.

To repeat both the DNA strand breaks and adduct work would require very large comprehensive studies to determine the nature of the adducts and the potential role of oxidative damage in their induction. I would recommend that the *in vitro* studies should take priority as they would provide valuable information relevant to the design of any *in vivo* adduct studies.