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Attorneys for Plaintiffs

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
This document relates to: ALL ACTIONS	

UNREDACTED VERSIONS OF PLAINTIFFS' MOTION TO COMPEL THE PRODUCTION OF ALL ORIGINAL AND RECUT SLIDES OF KIDNEY TISSUE FROM MICE IN STUDY BDN-77-420 AND EXHIBITS 1 AND 4 PURSUANT TO PTO #25

Pursuant to the Court's Pretrial Order #25, entered on June 6, 2017 (ECF No. 330), attached hereto are un-redacted versions of Plaintiffs' Motion to Compel the Production of all Original and Recut Slides of Kidney Tissue from Mice in Study BDN-77-420 and Exhibits 1 and 4 to said Motion originally filed on April 21, 2017 (ECF No. 256-2).

Dated: June 8, 2017

Respectfully Submitted,

/s/ Aimee Wagstaff

Aimee Wagstaff, SBN 278480
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Co-Lead Plaintiffs' Counsel
For MDL 2741

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing document was filed with the Court and electronically served through the CM-ECF system which will send a notification of such filing to all counsel of record. .

DATED: June 8, 2017

/s/ Aimee Wagstaff
ANDRUS WAGSTAFF, PC
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EXHIBIT 1

Monsanto

Monsanto Company
1101 17th Street, N. W.
Washington, D. C. 20036
Phone: (202) 452-8860

March 13, 1985

Mr. Douglas D. Campt
Director, Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, Virginia 22702

Subject: Roundup® Herbicide
EPA Reg. Nos. 524-308,
524-330, 524-339, 524-332
524-343
[redacted]

Dear Mr. Campt:

As part of a program to replace IBT toxicology studies Monsanto conducted a chronic feeding study with glyphosate in mice. Dietary levels of [redacted] were used in this [redacted] study. Even though the highest feeding level was equivalent to 3% glyphosate in the diet, no major chronic effects were observed nor were there any treatment related oncogenic effects noted. This study was [redacted] Upon completion of its review, the Agency indicated concern over a very low incidence of microscopic renal adenomas observed in high dose male mice. The incidence data were 0, 0, 1, 3 for control, low-dose, mid-dose, and high dose levels, respectively, and are not statistically significant at the 99% confidence level.

[redacted] in response to a request by the Agency, we submitted historical control data from the laboratory which performed the study as well as two other major contract laboratories. The data indicated that this lesion does occur occasionally and in comparable ranges.

[redacted] Dr. Lyle Gingerich, Dr. Fred Johannsen and I met with Drs. Farber and Burnam of the EPA. We had a full exchange of opinions at this meeting and appreciated the opportunity to explore the EPA position on glyphosate with them.

In the course of our meeting, however, it became clear that the EPA considers the results of the mouse study to be positive and that glyphosate should be categorized as a "possible" human carcinogen, acknowledging that the weight of the evidence for this conclusion is weak.

We continue to believe that the results of the chronic mouse study do not support the conclusion of a treatment-related oncogenic effect. The purpose of this letter is to summarize the scientific basis for our position and to provide additional interpretation and information for your consideration.

A. Inconsistency With Treatment-Related Etiology

1. Sex-specific Occurrence

Renal adenomas were only observed in male and not female mice following 2 years of glyphosate treatment. Significantly, and perhaps not considered by the EPA, was the fact that female mice in the high-dose group took in fully 20% more glyphosate on an mg/kg/day basis than their male counterparts (4232-9859 mg/kg/day in females vs. 3465-7220 mg/kg/day in males). If this lesion were treatment-related, one would have expected a dose-dependent increase in tumor development. This obviously did not occur because no females on test developed a renal adenoma.

2. No Time Course to Tumor Development

The small incidence of renal tumors seen in male mice possessed no normal time course to tumor development. Lesions were only observed in terminally sacrificed animals, while none were found in animals which died before the end of the 24 month study period. This observation supports the contention that these lesions were age-related rather than treatment related because a decreased time-to-tumor interval would have been expected had the latter been the case.

3. No Progression of Neoplastic Lesion

Only benign, not malignant, renal tumors were observed in aged male mice. Additionally, these lesions were found only unilaterally with no evidence of multiplicity of form. Had this effect been treatment related, a progression towards carcinomas formation and a multiplicity of sites would have been expected, especially in senile mice.

4. No Evidence to Support a Preneoplastic Effect

In contrast to thoughts expressed by the EPA at our February 21 meeting, [redacted] In fact, no such effects were observed in groups of mice fed glyphosate at a dose level of 50,000 ppm for up to 3 months; report submitted in May 1980, accession number 242799. Similarly, evaluation in a broad range of mutagenicity assays designed to assess point mutations, DNA damage or chromosomal effects in mammalian and bacterial cell systems uniformly resulted in a complete lack of geno-toxicity.

5. Specie Specificity

Results of a previously submitted 2-year rat study clearly established that there were [redacted]

A. Consistency With Spontaneous Etiology

1. Lack of Statistical Significance

The original analysis of multiple comparison of renal tumors between control and treated groups was conducted using the chi-square test for homogeneity. The significance level, or p-value, obtained from this test was 0.1241 (corrected) and 0.0408 (uncorrected). The corrected chi-square is essentially the same test but with a correction factor designed to improve the approximation. More imprtantly, the more widely accepted Fisher's Exact Test gives a p-value of 0.1249. [redacted]

Analysis of the data by the [redacted] for linear dose-response trends gives a [redacted] Theoretically, a finding of either one less tumor in the high dose group or one tumor in the control or low-dose group results in lack of statistical significance at the p=0.05 level. See Table on page 4 of this letter. Most importantly, [redacted]

Number of Tumors at Dose				Cochran Armitage Test
0	1000 ppm	5000 ppm	30,000 ppm	p-Value
0	0	1	3	0.016 .01
1	0	1	3	0.068
0	1	1	3	0.063
0	0	1	2	0.239

2. Within Range (%) of Historical Values

While the mean incidence of renal adenomas in large groups of male mice is quite low, Monsanto has supplied historical control data indicating a range of 0.0%-7.1% in individual study populations. Since the glyphosate male control group did not contain an animal with a renal tumor it obviously was at the low end of the range. The incidence of renal adenomas in high dose male mice were within, albeit at the high end, of the historical range of 7.1% for adenomas. The fact that no carcinomas were observed in any test group puts all four groups at the lowest end (0.0%) of the historical range for this tumor delineation.

3. Spontaneously Occurring Tumors Appear to be Sex Specific

Based on literature surveyed and historical control data gathered, [redacted] in male not female mice of the CD-1 strain. The fact that the renal adenomas seen in this study were also seen only in males, not females (even though females consumed a higher total glyphosate intake in this study), is consistent with the data available on the spontaneous occurrence of this tumor type.

In summary, [redacted] This conclusion has been reached not only by Monsanto scientists but by regulatory agencies worldwide.

As you know, Roundup is an extremely important herbicide to agriculture in the U. S. and around the world. Monsanto is concerned that even the initiation of formal regulatory action would have serious negative economic repercussions

which we believe are not justified by the scientific evidence. Therefore, [redacted] Furthermore, [redacted]

Thank you for your consideration of our request. Monsanto places high priority on the satisfactory resolution of this matter and we look forward to your response.

Should you have any questions, please contact Dr. Chester Dickerson or Mr. Lyle Gingerich of our Washington office or me.

Sincerely,

Frank S. Serdy
Manager, Federal and State
Registration Affairs

/pt

cc: Mr. Lyle L. Gingerich/Dr. Chester T. Dickerson, Jr.
Dr. J. Akerman
Dr. T. Farber
Mr. R. J. Taylor

bcc: E. E. Debus
R. L. Harness
T. F. Armstrong
R. W. Street
F. R. Johannsen
T. W. Fuhremann

Monsanto

Monsanto Company
1101 17th Street, N. W.
Washington, D. C. 20036
Phone: (202) 452-8860

March 13, 1985

Mr. Douglas D. Campt
Director, Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, Virginia 22702

Subject: Roundup® Herbicide
EPA Reg. Nos. 524-308,
524-330, 524-339, 524-332
524-343
Chronic Mouse Study with
Glyphosate

Dear Mr. Campt:

As part of a program to replace IBT toxicology studies Monsanto conducted a chronic feeding study with glyphosate in mice. Dietary levels of 0, 1000, 5000, and 30,000 ppm were used in this two year oncogenicity study. Even though the highest feeding level was equivalent to 3% glyphosate in the diet, no major chronic effects were observed nor were there any treatment related oncogenic effects noted. This study was submitted to the Agency in August, 1983. Upon completion of its review, the Agency indicated concern over a very low incidence of microscopic renal adenomas observed in high dose male mice. The incidence data were 0, 0, 1, 3 for control, low-dose, mid-dose, and high dose levels, respectively, and are not statistically significant at the 99% confidence level.

In March, 1984, in response to a request by the Agency, we submitted historical control data from the laboratory which performed the study as well as two other major contract laboratories. The data indicated that this lesion does occur occasionally and in comparable ranges.

On February 21, 1985, Dr. Lyle Gingerich, Dr. Fred Johannsen and I met with Drs. Farber and Burnam of the EPA. We had a full exchange of opinions at this meeting and appreciated the opportunity to explore the EPA position on glyphosate with them.

In the course of our meeting, however, it became clear that the EPA considers the results of the mouse study to be positive and that glyphosate should be categorized as a "possible" human carcinogen, albeit acknowledging that the weight of the evidence for this conclusion is weak.

We continue to believe that the results of the chronic mouse study do not support the conclusion of a treatment-related oncogenic effect. The purpose of this letter is to summarize the scientific basis for our position and to provide additional interpretation and information for your consideration.

A. Inconsistency With Treatment-Related Etiology

1. Sex-specific Occurrence

Renal adenomas were only observed in male and not female mice following 2 years of glyphosate treatment. Significantly, and perhaps not considered by the EPA, was the fact that female mice in the high-dose group took in fully 20% more glyphosate on an mg/kg/day basis than their male counterparts (4232-9859 mg/kg/day in females vs. 3465-7220 mg/kg/day in males). If this lesion were treatment-related, one would have expected a dose-dependent increase in tumor development. This obviously did not occur because no females on test developed a renal adenoma.

2. No Time Course to Tumor Development

The small incidence of renal tumors seen in male mice possessed no normal time course to tumor development. Lesions were only observed in terminally sacrificed animals, while none were found in animals which died before the end of the 24 month study period. This observation supports the contention that these lesions were age-related rather than treatment-related because a decreased time-to-tumor interval would have been expected had the latter been the case.

3. No Progression of Neoplastic Lesion

Only benign, not malignant, renal tumors were observed in aged male mice. Additionally, these lesions were found only unilaterally with no evidence of multiplicity of form. Had this effect been treatment related, a progression towards carcinomas formation and a multiplicity of sites would have been expected, especially in senile mice.

4. No Evidence to Support a Preneoplastic Effect

In contrast to thoughts expressed by the EPA at our February 21 meeting, no evidence of renal hyperplasia or inflammatory changes suggestive of a preneoplastic effect were seen in male mice from this study. In fact, no such effects were observed in groups of mice fed glyphosate at a dose level of 50,000 ppm for up to 3 months; report submitted in May 1980, accession number 242799. Similarly, evaluation in a broad range of mutagenicity assays designed to assess point mutations, DNA damage or chromosomal effects in mammalian and bacterial cell systems uniformly resulted in a complete lack of geno-toxicity.

5. Specie Specificity

Results of a previously submitted 2-year rat study clearly established that there were no treatment-related renal tumors in that test species.

A. Consistency With Spontaneous Etiology

1. Lack of Statistical Significance

The original analysis of multiple comparison of renal tumors between control and treated groups was conducted using the chi-square test for homogeneity. The significance level, or p-value, obtained from this test was 0.1241 (corrected) and 0.0408 (uncorrected). The ~~uncorrected~~ corrected chi-square is essentially the same test but with a correction factor designed to improve the approximation. More imprtantly, the more widely accepted Fisher's Exact Test gives a p-value of 0.1249. Thus, by either the Fisher's Exact test or chi-square (corrected) test the tumor incidence data are not significant at the p equals 0.05 level.

Analysis of the data by the Cochran-Armitage test for linear dose-response trends gives a p-value of 0.016. Theoretically, a finding of either one less tumor in the high dose group or one tumor in the control or low-dose group results in lack of statistical significance at the p=0.05 level. See Table on page 4 of this letter. Most importantly, the lack of any complementary or confirming evidence of a treatment relationship for this tumor, as discussed previously with EPA and in this letter, casts doubt on the likelihood of any dose-response relationship.

Number of Tumors at Dose				Cochran Armitage Test
0	1000 ppm	5000 ppm	30,000 ppm	p-Value
0	0	1	3	0.016
1	0	1	3	0.068
0	1	1	3	0.063
0	0	1	2	0.239

2. Within Range (%) of Historical Values

While the mean incidence of renal adenomas in large groups of male mice is quite low, Monsanto has supplied historical control data indicating a range of 0.0%-7.1% in individual study populations. Since the glyphosate male control group did not contain an animal with a renal tumor it obviously was at the low end of the range. The incidence of renal adenomas in high dose male mice were within, albeit at the high end, of the historical range of 7.1% for adenomas. The fact that no carcinomas were observed in any test group puts all four groups at the lowest end (0.0%) of the historical range for this tumor delineation.

3. Spontaneously Occurring Tumors Appear to be Sex Specific

Based on literature surveyed and historical control data gathered, renal tumors have only been seen spontaneously in male not female mice of the CD-1 strain. The fact that the renal adenomas seen in this study were also seen only in males, not females (even though females consumed a higher total glyphosate intake in this study), is consistent with the data available on the spontaneous occurrence of this tumor type.

In summary, Monsanto strongly believes that the overwhelming weight of evidence available supports the position that the incidence of renal adenomas in this study is unrelated to treatment. This conclusion has been reached not only by Monsanto scientists but by regulatory agencies worldwide.

As you know, Roundup is an extremely important herbicide to agriculture in the U. S. and around the world. Monsanto is concerned that even the initiation of formal regulatory action would have serious negative economic repercussions

which we believe are not justified by the scientific evidence. Therefore, we request that you inform us of the next steps EPA intends to take on the review of glyphosate. Furthermore, if, on the basis of the chronic mouse study, the Agency intends to move toward regulation of glyphosate, we request the opportunity to meet with Messrs. Campt and Melone to discuss further our position.

Thank you for your consideration of our request. Monsanto places high priority on the satisfactory resolution of this matter and we look forward to your response.

Should you have any questions, please contact Dr. Chester Dickerson or Mr. Lyle Gingerich of our Washington office or me.

Sincerely,

Frank S. Serdy
Manager, Federal and State
Registration Affairs

/pt

cc: Mr. Lyle L. Gingerich/Dr. Chester T. Dickerson, Jr.
Dr. J. Akerman
Dr. T. Farber
Mr. R. J. Taylor

MAY 16 1985

MARVIN KUSCHNER, M. D.
64 EAST GATE DRIVE
HUNTINGTON, N. Y. 11743

TELEPHONE (516) 367-4811

May 11, 1985

Timothy J. Long, Ph.D.
Senior Product Toxicologist
Monsanto Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167

Dear Doctor Long:

At your request I have examined the sections of mouse kidneys in Project No. M-6 77-2061. Individual slides were derived from animals 1001 through 4550 with the exception of animal 1016 which was noted to be missing.

This first examination was undertaken to: (1) attempt to illuminate the morphogenesis of neoplasms by identifying pre-neoplastic changes; (2) seek for evidence of cytotoxic effects that might suggest a promoting action of the test material; (3) determine the presence or absence of epithelial neoplasia. The incidence of lymphomatous infiltration and non-neoplastic changes such as amyloidosis, pyelonephritis, renal abscesses, and multicystic change were not recorded by me although noted to be of common occurrence in all groups.

Evidence of pre-neoplastic change and of cytotoxic effects were not found.

The neoplasms noted were as follows:

Group I M - Animal 1028

Group III M - Animal 3023

Group IV M - Animals 4029; 4032; 4041

These tumors were all of the renal cortical epithelial type. In animals 1028 and 4029 the tumors were minute (1mm or less) and were apparently not observed grossly. Tumors in the remaining 3 animals were large and seen grossly. The largest of these (#3023) showed most evidence of atypicality. There seems to be little point to classifying this tumor as malignant and the others as benign since it would appear that all these have the potential for enlargement, anaplasia, and peripheral invasion. No distinguishing histological characteristics of malignancy have been identified.

MARVIN KUSCHNER, M. D.
64 EAST GATE DRIVE
HUNTINGTON, N. Y. 11743

TELEPHONE (516) 367-4811

The single tumor in the control animal (#1028) is of the so-called "clear-cell" type. All others are predominantly of the "dark-cell" variety although one (#4032) has "clear-cell" components. I know of no biological distinction between these types.

Sincerely yours,

Marvin Kuschner, M.D.
MK/kp

EXHIBIT 4

12/4/85

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

December 4, 1985

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: William Dykstra, Ph.D.
Reviewer, Toxicology Branch, TS-769

FROM: Louis Kasza, D.V.M., Ph.D. L K.
Pathologist, Toxicology Branch, TS-769

SUBJECT: Glyphosphate — Evaluation of Kidney Tumors in Male Mice. Chronic Feeding Study.

INTRODUCTION:

Tumors (0 (1)*; 0; 1; 3) were found in the kidneys of male mice at different dose levels. There were differences in the pathologists' opinions as to whether the small localized change in one kidney of the control group (#1028) represented a tumor or not. In order to provide more information, the Agency recommended the preparation of three (3) additional sections from each kidney in the male groups. "The lesion was not present in the recut specimens from that animal" in the control group (#1028). In the final re-evaluation of the questionable control kidney slides (#1028), the conclusion was formulated that "The pathology staff at Bio/dynamics and I (Dr. McConnell) reviewed the lesion and concur that it may be representative of a developing tumor".

MATERIALS AND METHODS:

I (Dr. Kasza, Branch Pathologist) requested all kidney sections from male mice. After selection of slides from all animals in which kidney tumors were diagnosed, I studied them under the microscope.

RESULTS:

There was no difference in diagnoses between my and other pathologists' diagnoses with respect to kidney tumors in mid- (#3023) and high dose (#4029, 4023, 4041) groups. With regard to the questionable male control kidney (#1028), it is my opinion that the presence of a tumor can not definitely be established. My interpretation is similar to the conclusion of Bio/dynamics' pathology staff and Dr. McConnell, that the lesion "may be" a proliferative change having the potential to lead to the development of a frank tumor. But as the tissue can be seen under the microscope as a small well-demarcated focal cell aggregate morphologically different from the healthy looking surrounding kidney tissue, this morphological alteration does not represent a pathophysiologically significant change.

*In parentheses is the review pathologist's findings.

cc: T. Farber
W. Burnam
R. Engler
R. Zendzian