Michael J. Miller (appearance *pro hac vice*)
Timothy Litzenburg (appearance *pro hac vice*)
Curtis G. Hoke (State Bar No. 282465)
**The Miller Firm, LLC**
108 Railroad Ave.
Orange, VA 22960
(540) 672-4224 phone; (540) 672-3055 fax
mmiller@millerfirmllc.com
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choke@millerfirmllc.com

*Attorneys for Plaintiff*
*DEWAYNE JOHNSON*



**SUPERIOR COURT OF THE STATE OF CALIFORNIA**

**FOR THE COUNTY OF SAN FRANCISCO**

DEWAYNE JOHNSON,

Plaintiff,

v.

MONSANTO COMPANY

Defendants.

Case No. CGC-16-550128

**DECLARATION OF CURTIS G. HOKE IN SUPPORT OF PLAINTIFF'S RESPONSE TO DEFENDANT'S MOTION IN LIMINE 24 TO EXCLUDE REFERENCE TO A MAGIC TUMOR**

Trial Judge: TBD

Trial Date: June 18, 2018
Time: 9:30 AM
Department: TBD

**DECLARATION OF CURTIS G. HOKE**

I, Curtis Hoke, declare and state:

1. I am an attorney at law admitted to practice before all of the courts in the state of California. I am an attorney at The Miller Firm, LLC, attorneys of record for Plaintiff Dewayne Johnson. I am over eighteen years of age and am fully competent to make this Declaration in support of Plaintiff's Opposition to Defendant's Motion in Limine No. 10 to Exclude Benbrook's Opinions Regarding Personal Protective Equipment. Except as otherwise expressly stated below, I have personal knowledge of the facts stated in this declaration, and if called to testify, I could and would competently testify to the matters stated herein.

2. Attached hereto as **Exhibit A** is a true and correct copy of MONGLY00246215, a document produced by Monsanto in discovery.

3. Attached hereto as **Exhibit B** is a true and correct copy of An April 3, 1985 Monsanto memo, MONGLY04277789, produced by Monsanto in discovery.

4. Attached hereto as **Exhibit C** is a true and correct copy of a fedex receipt, MONGLY04269049 produced by Monsanto in discovery.

5. Attached hereto as **Exhibit D** is a true and correct copy of an April 3, 1987 letter from Monsanto MONGLY04278109, produced by Monsanto in discovery

6. Attached hereto as **Exhibit E** is a true and correct copy of an August 20, 1985 Monsanto Memo MONGLY04268982, produced by Monsanto in discovery.

7. Attached hereto as **Exhibit F** is a true and correct copy of portions of California's Final Statement of Reasons for Setting the NSRL level for Glyphosate.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Executed on June 7, 2018 in Orange, Virginia.

By: _____
Curtis G. Hoke,
Declarant

# EXHIBIT A

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 Serdy

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.

# EXHIBIT B

Monsanto

f-glyphosate

FROM (NAME—LOCATION—PHONE) Dept. of Medicine & Environmental Health G.J. Levinskas, G2WF 4-8809

DATE : April 3, 1985 cc: G. Roush, Jr., M.D.

SUBJECT :

REFERENCE :

TO : T.F. Evans

The following item of information is in addition to those included in the current monthly report.

Senior management at EPA is reviewing a proposal to classify glyphosate as a class C "possible human carcinogen" because of kidney adenomas in male mice. Dr. Marvin Kuschner will review kidney sections and present his evaluation of them to EPA in an effort to persuade the agency that the observed tumors are not related to glyphosate.

George J. Levinskas

GJL/sfd

IN-10-M (REV. 10/83)

# EXHIBIT C

Bio/dynamics Inc.

APR 9 1985

April 3, 1985

Dr. Marvin Kushner
64 East Gate Drive
Huntington, New York 11743

Re: 77-2061

Dear Dr. Kushner:

The enclosed shipment is being sent to you at the request of Dr. Tim Long of Monsanto. It contains slides of kidney sections from all animals on the referenced study. As indicated on the inventory records, a number of the slides also contain sections of urinary bladder.

If you have any questions concerning this shipment, please do not hesitate to contact me.

Sincerely,

A. L. Knezevich

Aleksandar L. Knezevich, Dr.Med.Vet.
Senior Vice-President, Pathology

nas
encls.
cc: Dr. Tim Long
Dr. Ira W. Daly

P.O. Box 43 • East Millstone, New Jersey 08873 • (201) 873-2550 • Telex: 844597 • Cable: BIO/DYN

File: glyphosate
BD-77-420

# HISTOPATHOLOGY LABORATORY RECEIPT

COMPANY CODE/PROJECT NUMBER: M-6 77-2061

REPORT TITLE/COMPOUND: A Chronic Feeding Study of Glyphosate in Mice

DESCRIPTION: 5 Slide boxes containing 422 slides representing 399 animals from Groups I, II, III & IV (Term and UD's) Sections of Kidneys. Also included is a list of animals showing Kidneys with Urinary Bladders.

Purpose: Sponsors Request

COMMENTS: NOTE: Animal Number 1016 is missing per Report.

SHIPPED TO: Dr. Marvin Kuschner

VIA: Federal Express

AUTHORIZED BY: for Bio/dynamics, Inc. Date

RECEIVED BY: Marvin Kuschner 4/14/85

NOTE TO RECEIVER: Please sign and return this form to Bio/dynamics, Inc., Attention: Pathology Department.

NOTE TO PATHOLOGIST: All tissues required by protocol to have histopathological evaluation must be accounted for. If any tissues are missing, please contact the Pathology Department ext. 213 immediately.

# EXHIBIT D

# Monsanto

**MONSANTO AGRICULTURAL COMPANY**
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167
Phone: (314) 694-1000

April 3, 1987

SB 950 Response
Pesticide Registration Branch
California Department of Food
and Agriculture
1220 N Street, Room A447
Sacramento, California 95814

Subject: Glyphosate
Reconsideration of Chronic/Oncogenicity
Mouse Study

Dear Sir:

Monsanto Agricultural Company requests the California Department of Food and Agriculture to reconsider the evaluation of the Chronic/Oncogenicity Study for Glyphoste in Mice (BD-77-420). CDFA has stated that a possible oncogenic effect is demonstrated and has placed the study in Group 3 of the Low Priority List for SB 950 Risk Assessment. Monsanto maintains that there is no treatment related oncogenic effect in this study -- a position supported by experts and regulatory agencies world wide. We hereby request the Department to reconsider this decision and are submitting additional information which clearly supports our position.

We have submitted the following data to CDFA:

1. Eight (8) volumes of data - which is the entire study.

2. Re-examination of male kidneys. These data revealed a tubular adenoma in mouse #1028 (control)

We understand that CDFA does not consider the finding in the control male as real. We had several expert toxicologists examine the slides and give their opinions. At this time, we are forwarding these opinions to CDFA.

EPA also requested that the Scientific Advisory Panel (SAP) review the data and give their opinion as to the classification of glyphosate as a possible human carcinogen. We are submitting the SAP decision at this time. We note that they concluded that the adenoma in the control is real, and that the results of this study do not demonstrate any oncogenic effect.

We are also submitting a copy of the FAO Plant and Protection Paper #77. The WHO Expert Group on Pesticide Residues reviewed all available toxicology data on glyphosate and reported that there is no evidence of carcinogenicity for glyphosate.

We feel that the submission of these additional reports emphasize that expert toxicologists world-wide do not believe that glyphosate is an oncogen. We request CDFA to remove glyphosate from the SB 950 Risk Assessment List based on the data previously submitted and the data submitted at this time.

Should you have questions, please feel free to contact Monsanto.

Sincerely,

Glynadee Edwards

Glynadee Edwards
Senior Registration Specialist

/jjs

Enclosures

bcc: J. H. Arvik
E. E. Debus
K. F. Cannon
T. J. Long

# EXHIBIT E

Monsanto

AUG 29 1985

FROM (NAME—LOCATION—PHONE) Lyle L. Gingerich - 1920

DATE : August 20, 1985

cc C. T. Dickerson, Jr./File

SUBJECT : Roundup S.A.P. Meeting

REFERENCE :

TO :

T. F. Armstrong - C2SC
E. E. Debus - C2SC
F. S. Serdy - C2SC

If the results of the kidney re-sectioning do not resolve the glyphosate issue within OPP, we will be faced with an adverse OPP decision. It is likely that OPP will ask the S.A.P. for concurrence on its determination that there is a treatment-related effect in the glyphosate mouse study.

I expect the questions to the S.A.P. will be narrowly crafted and we will have a minimal time to prepare a response to the questions. The EPA's intention to take no regulatory action should work in their favor. The S.A.P. could reluctantly agree that there is a treatment-related effect and take comfort in the fact that no action is planned over such an insignificant risk.

Can we change the focus of the questions to the S.A.P. to: "Is 30,000 ppm too high to be used in a meaningful risk assessment?". Do we have examples of any other pesticide being fed at such a high level? If we assembled 10 respected toxicologists, would all ten agree that the feeding level is too high to be meaningful?

If so, I recommend that we bring all ten of the toxicologists to the S.A.P. meeting. There is a tendency to "count the votes" at S.A.P. meetings. We can make a difference by lining up a large number of experts on our side.

Dr. Moore and Dr. Farber may be misreading the consensus of their professional colleagues on this issue. With the importance of this decision to Monsanto, I don't think we can leave any doubt in the minds of the EPA or the S.A.P. of what the consensus of the professional toxicologists is on this issue.

I would also recommend that we place the names of each of our supporting toxicologists on the written agenda for the S.A.P. meeting. All of the S.A.P. members read the agenda and would take note of the names of the persons supporting our position.

Lyle L. Gingerich

/ms

IN - 10 (REV. 8/77)

Monsanto

16 2 9 1985

FROM (NAME—LOCATION—PHONE) E. J. Brandt C2SM 4-5408

DATE : August 27, 1985

SUBJECT :

REFERENCE :

cc: A. G. Barnett/C2SD
D. K. Flaherty/EHL
L. D. Kier/EHL
T. J. Long/G2WD
W. E. Ribelin/EHL

TO : E. E. Debus/C2SC

On August 27, a meeting was held (attendees - Brandt, Flaherty, Kier, Long) to explore the potential role of immune system dysfunction in development of observed kidney pathology in male CD-1 mice exposed long-term to high levels of glyphosate in their diet. After considerable discussion, it was concluded that:

1. Another meeting of the group should be convened after the results of the ongoing slide re-reading are available (late September).

2. Pending the outcome of the slide re-reading, the group will determine whether or not it would be useful to prepare a draft research proposal designed to address the occurrence of kidney tumors in CD-1 mice from an immunologic perspective.

3. In the interim, various technical questions which surfaced during our meeting discussions will be searched in order to help expedite development of a research proposal should one be considered appropriate after the slide re-reading results are known.

I will keep you appraised of our activities in this area.

E. J. Brandt

/ac

EJB2/8/27/85

IN 1120

# EXHIBIT F

# FINAL STATEMENT OF REASONS
# TITLE 27, CALIFORNIA CODE OF REGULATIONS

## SECTION 25705(b) SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

## NO SIGNIFICANT RISK LEVEL: GLYPHOSATE

This is the Final Statement of Reasons for the adoption of a No Significant Risk Level (NSRL)[1] for glyphosate. On June 26, 2017, the Office of Environmental Health Hazard Assessment (OEHHA) announced the listing of glyphosate, effective July 7, 2017, as a chemical known to the state to cause cancer for purposes of Proposition 65[2]. OEHHA issued a Notice of Proposed Rulemaking to adopt a proposed amendment to Section 25705, Specific Regulatory Levels Posing No Significant Risk, identifying an NSRL of 1100 micrograms per day (µg/day) for glyphosate under Title 27, California Code of Regulations, section 25705(b)[3]. The Initial Statement of Reasons sets forth the grounds for the amendment to the regulation.

Briefly, in developing the NSRL for glyphosate, OEHHA relied on Volume 112 in the series of International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, entitled "Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos"[4], which summarizes the available data from rodent carcinogenicity studies of glyphosate, as well as other information relevant to the carcinogenic activity of this chemical. The NSRL is based upon the results of the most sensitive scientific study deemed to be of sufficient quality[5]. OEHHA agrees with IARC's determination that the increased incidence of hemangiosarcomas observed in a study of male CD-1 mice is treatment-related and is using that study as the basis for the NSRL.

---

[1] No Significant Risk Levels (NSRLs) for cancer-causing chemicals have been established for many of the chemicals listed under Proposition 65. A business would not be required to provide a Proposition 65 warning for an exposure to a listed carcinogen that is at or below the NSRL.

[2] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 *et. seq.*, hereafter referred to as "Proposition 65" or "The Act".

[3] All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.

[4] International Agency for Research on Cancer (IARC, 2015). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112, Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France. Available from: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php

[5] Section 25703(a)(4)

**Response 2:** These comments all appear to be based on an *in vitro* study by Thongprakaisang et al. (2013)[22], in which glyphosate was shown to induce proliferation in a hormone-dependent human breast cancer cell line (T47D cells derived from ductal carcinoma cells), but not in a hormone-independent human breast cancer cell line (MDA-MB231 breast adenocarcinoma cells). This study is not a human epidemiology study and thus it does not provide evidence that glyphosate induces breast cancer in humans. Rather, it is a study of the effect of glyphosate on the proliferation of cultured cells, and it does not provide information that can be used to derive the NSRL for glyphosate. No changes were made to the regulatory proposal based on this comment.

**Comment 3 (Monsanto, Ramboll Environ on behalf of The Scotts Company LLC, and others):** Reviews by others have concluded that there are no treatment-related tumors in animal cancer bioassays of glyphosate, nor are there other datasets that provide evidence of a strong dose-response relationship of carcinogenicity that could be relied upon to estimate the potential for health effects in humans following exposure to expected concentrations and that the lack of an adequate dataset is consistent with conclusions reached by JMPR (2006) and US EPA (2016) that any tumor findings are not treatment-related. OEHHA has no basis to quantify an NSRL using experimental animal studies.

**Response 3:** Glyphosate was listed under Proposition 65 via the "Labor Code" listing mechanism, based on IARC's classification[23] of glyphosate as *probably carcinogenic to humans* (Group 2A), and its conclusion that there is *sufficient evidence* of carcinogenicity in experimental animals for glyphosate. IARC's conclusion of sufficient evidence in experimental animals is based on findings from two studies in male mice. Specifically, IARC cited "a significant positive trend in the incidence of haemangiosarcoma [a malignant neoplasm] in male CD-1 mice" in a two-year diet study[24], and "a positive trend in the incidence of renal tubule carcinoma [a malignant neoplasm] and of renal tubule adenoma and carcinoma (combined) [an appropriate combination of benign and malignant neoplasms]" in male CD-1 mice in a different

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[22] Thongprakaisang S, Thiantanawat A, Rangkadilok N, Suriyo T, Satayavivad J., 2013. Glyphosate induces human breast cancer cells growth via estrogen receptors. *Food Chem Toxicol* **59**:129-36.
[23] IARC (2015). Full citation provided in footnote 3.
[24] As noted in the Initial Statement of Reasons, this study of glyphosate (purity 98.6%) met the criterion in Section 25703 as the most sensitive study of sufficient quality, and was used to derive the NSRL. This study was performed by Inveresk Research International and summarized in the 2006 Joint FAO/WHO Meeting on Pesticide Residues report (JMPR, 2006. Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva: World Health Organization; pp. 95 – 169.) and by IARC (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).

two-year diet study[25], with IARC noting that these malignant kidney tumors are rare in this strain of mice. OEHHA agrees with IARC's determination that these tumor findings are treatment-related and demonstrate statistically significant dose-response relationships.

In developing the NSRL for glyphosate, OEHHA followed the guidance set forth in Section 25703 that the assessment "be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical as known to the state to cause cancer", and based the NSRL on the results of the most sensitive scientific study deemed to be of sufficient quality. OEHHA determined that the two-year study conducted in male CD-1 mice fed glyphosate (purity 98.6%) in the diet, in which a significant positive trend in the incidence of hemangiosarcomas was observed, met the criteria in 25703 as the most sensitive study of sufficient quality. OEHHA used this data to derive the NSRL for glyphosate. No changes were made to the regulatory proposal based on this comment.

**Comment 4 (Monsanto):** The commenter cited the decision in *Baxter Healthcare Corp. v. Denton,* 120 Cal. App. 4th 333, 15 Cal. Rptr. 3d 430 (2004) to support its assertion that OEHHA is required to determine that a glyphosate exposure at any level does not pose a "significant risk", and as such requires OEHHA to establish an "infinite" NSRL. Baum, Hedlund, Aristei & Goldman, P.C. and others stated that Monsanto's reliance on *Baxter v. Denton* is inappropriate.

**Response 4:** OEHHA disagrees that the *Baxter* decision mandates the establishment of an infinite NSRL. The decision in *Baxter* is factually distinguishable from the proposed NSRL for glyphosate[26]. The commenter provides no evidence that the mechanism of action for glyphosate does not operate in humans, which was the pivotal issue in that case. In *Baxter*, the Appellate Court focused on evidence that the mechanism by which DEHP increased the incidence of liver tumors in animals was not relevant to humans[27]. This notably included evidence regarding the classification of DEHP by IARC[28]. At the time of the *Baxter* decision, IARC had downgraded its earlier classification of DEHP as Group 2B ("possibly carcinogenic to humans") to Group 3 ("not classifiable as to its carcinogenicity to humans"). Glyphosate, on the other hand,

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[25] In summarizing this study of glyphosate (purity 99.7%), IARC cited four US EPA documents (US EPA 1985a, b, 1986, 1991a) (IARC, 2015, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos. IARC, World Health Organization, Lyon, France).
[26] See comment letters from Baum, Hedlund, Aristei & Goldman, P.C., (Comment #9945) and Center for Biological Diversity, et al. (Comment #9974)]
[27] Baxter Healthcare Corp. v. Denton, 120 Cal. App. 4th 333, 15 Cal. Rptr. 3d 430 (2004), at 438.
[28] *Id.*

> "Animal bioassay studies for quantitative risk assessment shall meet generally accepted scientific principles, including the thoroughness of experimental protocol, the degree to which dosing resembles the expected manner of human exposure, the temporal exposure pattern, the duration of study, the purity of test material, the number and size of exposed groups, the route of exposure, and the extent of tumor occurrence."

As can be seen in the full quotation of Section 25703(a)(1) above, "the degree to which dosing resembles the expected manner of human exposure" is one of *several* key considerations in determining whether or not an animal cancer bioassay is suitable for use in the development of an NSRL. OEHHA found the data used to derive the NSRL for glyphosate to be sufficient with respect to each of these considerations. With regard to the manner in which animals were dosed, diet is one of the expected routes of glyphosate exposure in humans and thus deriving the NSRL from study data in which test animals were administered glyphosate through the diet is consistent with the regulations. Animal bioassays employing dietary exposure are commonly used and routinely accepted for toxicity testing of pesticides.

**Comment 19 (Dr. Thomas McDonald):** OEHHA should make its own determination on the genotoxicity of glyphosate and not rely on IARC. He states that other authoritative bodies have concluded that glyphosate poses no genotoxicity risk in mammals, and that a Margin of Exposure (MOE) approach [to dose-response assessment] appears more appropriate.

**Response 19:** To the extent that the comment is directed toward the listing of glyphosate, it is not relevant to the determination of an NSRL for this chemical. OEHHA has reviewed the discussion of the mechanistic data for glyphosate provided in the IARC monograph and agrees with IARC's conclusion that "Overall, the mechanistic data provide strong evidence for genotoxicity and oxidative stress. There is evidence that these effects can operate in humans."[70]

OEHHA notes that IARC[71] further elaborated on this evidence, stating:

- "There is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans in vitro and studies in experimental animals. One study in several communities in individuals exposed to glyphosate-based formulations also found chromosomal damage in blood cells; in this study, markers of chromosomal damage (micronucleus formation)

[70] IARC (2015) p. 78, full citation provided in footnote 3.
[71] IARC (2015) pp. 78-79, full citation provided in footnote 3.

were significantly greater after exposure than before exposure in the same individuals."

- "There is strong evidence that glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid can act to induce oxidative stress based on studies in experimental animals, and in studies in humans in vitro. This mechanism has been challenged experimentally by administering antioxidants, which abrogated the effects of glyphosate on oxidative stress. Studies in aquatic species provide additional evidence for glyphosate-induced oxidative stress."

OEHHA disagrees that a Margin of Exposure approach is more scientifically appropriate for derivation of the NSRL for glyphosate than the procedure used by OEHHA. Section 25703 sets forth a default approach, using a multistage model for deriving a cancer potency estimate, which is used "in the absence of principles or assumptions scientifically more appropriate"[72]. No information has been provided in support of another mechanism of action that would suggest a different approach to dose-response analysis.

In deriving the NSRL, OEHHA used the Benchmark Dose (BMD) method, as described both in OEHHA's guidance[73] and in the US EPA guidelines[74], applying a multistage mathematical model to describe the relationship between the risk of cancer and the dose. As part of the procedure OEHHA used for determining the cancer potency using the BMD method, a determination is made as to the proper type of extrapolation from the point of departure (typically the 95% lower confidence limit of the $ED_{05}$ or $ED_{10}$ for tumor induction) to low doses. OEHHA considered whether there was a more scientifically appropriate method for the NSRL derivation than linear extrapolation, but did not identify one, stating in the Initial Statement of Reasons:

> "Based on consideration of the available mechanistic information on glyphosate and the above conclusions reached by IARC[75], a multistage model is applied to derive a cancer potency estimate, following the guidance in Section 25703. There are no principles or assumptions scientifically more appropriate, based on the available data, than this approach."[76]

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[72] Section 25703(a)
[73] OEHHA (2009). Technical Support Document for Cancer Potency Factors. Available from: https://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf
[74] US EPA (2005). Guidelines for Carcinogen Risk Assessment, March 2005. Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.
[75] IARC (2015). Full citation provided in footnote 3.
[76] OEHHA (2017). Initial Statement of Reasons, Title 27, California Code of Regulations, Proposed Amendment to: Section 25705(b) Specific Regulatory Levels Posing No Significant Risk. Glyphosate. Available at https://oehha.ca.gov/media/downloads/crnr/glyphosate032917isor.pdf