EXHIBIT 96

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	

REBUTTAL REPORT OF DR. CHRISTOPHER J. PORTIER

IN SUPPORT OF GENERAL CAUSATION

ON BEHALF OF PLAINTIFFS

This rebuttal report addresses the reports of Dr. Corcoran and Dr. Foster. Because they address different issues, I address their statements separately, Dr. Corcoran first and Dr. Foster second. I do not address each issue with which I disagree; rather I identify those that I understand are appropriate for rebuttal.

REBUTTAL TO DR. CORCORAN

I. INTRODUCTION

Dr. Corcoran, in his response to my evaluation of glyphosate, demonstrates a lack of understanding of and experience with animal carcinogenicity studies. In addition, he seems to have missed some of the critical points that were made in my Expert Report, dated June 27, 2017 (hereinafter "Expert Report"). Further, he suggests an alternate analysis of the pooled data than the one I used in the Expert Report; this alternate analysis is also based on sound statistical methodology and when applied to the data set at issue here, yields effectively identical results to those in the Expert Report. These points are addressed below.

II. RESPONSE TO DR. CORCORAN'S p-VALUE COUNT

Dr. Corcoran claims that there are 1,016 p-values evaluated in the 12 animal bioassays considered acceptable for the evaluation. (Corcoran Report, at p. 9 & Tables 1 and 2). He arrives at this number by his evaluation of every neoplastic endpoint provided in the tables by **Greim et al. (2015)**[1]. Where did these 1,016 p-values come from?

Primary tumors are cancers that develop at the anatomical site where the cancer begins. Many cancers, after developing at their primary site, can metastasize and invade other anatomical sites leading to what are referred to as secondary or metastatic tumors. In evaluating the potential for a chemical to cause cancer, the predominant interest is in the increased incidence of primary tumors, not increases in secondary tumors that arise in one place (e.g. the liver) and metastasize to invade another organ (e.g. the lung). Tumors have a specific signature, so secondary tumors found in the lung that arose from the liver will be identified as a metastatic tumor in the lung but generally would not be included in an analysis of primary tumors. Eighty-one (81) of the tumor sites appearing in Dr. Corcoran's Tables A.1-7 and B.1-5 in his Appendix are metastatic secondary tumors and should not be included in the p-value count for this analysis.

Some tumors in animal bioassays are organ-specific (e.g. hepatocellular carcinomas in liver) and some are systemic (e.g. malignant lymphomas). Systemic tumors are not analyzed separately; instead, results are combined and a single analysis is conducted on the combined results. Thus, an analysis of malignant lymphomas that are found in the lung would not be done separately from those found in a particular lymph node. There are numerous examples in Dr. Corcoran's analysis where he fails to combine systemic tumors. Instead, Dr. Corcoran erroneously conducts multiple individual analyses. Engaging in this type of data analysis is incorrect, inflates the total p-values evaluated, and fails to appreciate the significance of the reported systemic tumors that

a combined analysis demonstrates. Of special importance are the malignant lymphomas, hemangiomas, and hemangiosarcomas in mice.

Some organs in the body are made up of pairs of separate organs (e.g. kidneys, lungs, ovaries). In some of the studies analyzed by Dr. Corcoran, tumors in these organs are presented as unilateral (affecting only one side of the body) or as bilateral (affecting both sides) with separate counts given for each category. It is uncommon to analyze these categories separately, and animals with either unilateral or bilateral tumors are simply grouped together as having the tumor. Similarly, for some of the studies, Dr. Corcoran also counts animals that have a single tumor of a specific type separately from animals with multiple tumors of that same type. These also should be combined in analyses where the interest is in whether an animal got a tumor of a specific type or did not. In both of these cases, by not combining the information into a single category, important chemical-related effects can be missed and the total number of p-values is inflated.

In every well-conducted animal bioassay, the pathology generally involves the evaluation of over 40 tissues in each sex/species group from the study. Given the different types of tumors in different tissues that might arise from such a study (e.g. thyroid follicular cell carcinomas and thyroid c-cell carcinomas), there is the potential to have more than 200 different evaluations of the data from each sex/species group. A majority of these potential tumor type-by-site combinations have no tumors. In addition, many sites have only one or two tumors in all of the animals evaluated; statistical tests simply cannot detect the effect of a chemical to increase tumors in cases where so few animals have a tumor. Without the use of historical control data, it is common practice not to evaluate the tumor sites with less than three tumors and only analyze those sites with three or more tumors.

Table 1 shows the total number of primary tumor sites evaluated by Dr. Corcoran, but adjusts his data to match common practice in analyzing cancer bioassays. Table 1 adds several tumor sites that were missed by Dr. Corcoran in his tables. Table 1 also eliminates secondary tumors, combines separate counts for unilateral and bilateral tumors, combines separate counts for single and multiple tumors and eliminates individual sites for systemic tumors using only one analysis for each systemic tumor. Once the data is adjusted to correct the omissions and analytical errors, the 1,016 p-values observed by Dr. Corcoran are shown to be an inflated count of tumor analyses. As exemplified in Table 1, there are 847 possible evaluations that could have been performed on these data. Of the possible evaluations, only 319 have three or more animals with tumors and, thus, should be analyzed.

III. APPROPRIATE USE OF HISTORICAL DATA

Dr. Corcoran criticizes the application of the numbers provided by Dr. Haseman in the Expert Report since historical control data was used to evaluate some of the studies, especially those in mice. Twenty sites were evaluated using historical control data and in exactly four of those sites, the historical data changed the resulting p-value from non-significant to significant. These four are kidney carcinomas (p_{Trend}=0.063, p_{Hist}=0.002) and adenomas and carcinomas

(p_{Trend}=0.065, p_{Hist}=0.011) in the study by **Knezevich and Hogan (1983)**[2], and kidney adenomas (p_{Trend}=0.062, p_{Hist}=0.005) and hemangiosarcomas (p_{Trend}=0.062, p_{Hist}=0.004) in the **Sugimoto (1997)**[3] study. In all four cases, the tumors are rare and all were at or close to the statistical limit of the exact trend test to identify an effect; this is the correct condition for historical control animals to make a difference in the analysis. Regardless, Dr. Corcoran implies that there is double the number of evaluations in the analysis because of the historical control evaluations. In fact, there are only 20 extra, 16 of which did not change the p-value at all.

Dr. Haseman's numbers are reasonable and come close to matching what is seen in the actual data. In male rats, there were on average 17.1 evaluations of single tumor findings in each study. Given that one would also combine tumor findings like liver adenomas and carcinomas, this is likely to add four to five additional analyses per bioassay giving 21 or 22 evaluations; Dr. Haseman chose 21.5. For female rats, there were an average of 13.4 analyses at individual sites and Dr. Haseman chose to use 25.5; this appears to be too high. Considering that females have a few more combined tumor analyses than males, I believe that 20 analyses in female rats would be more appropriate than 25.5; **Modified Table 15** (Appendix) now uses 20 tests for female rats. For male and female mice, the averages are 8.4 and 12.6, respectively, with Dr. Haseman choosing to use 10.5 and 15, again in reasonable agreement with the data. Using this arithmetic, a total of 418 possible evaluations would be done in all of these studies combined (**Modified Table 15**, Appendix), allowing almost 100 more sites than the actual count of sites with three or more animals shown in **Table 1**.

Dr. Corcoran criticizes the test used for the historical control analyses on the grounds that it does not take into account the heterogeneity that might exist across the various control groups. He references several other methods based upon statistical literature. There are several problems with this suggestion. In many cases, the methods outlined by Dr. Corcoran require the individual tumor counts from each historical control group; in many cases, only the average of the data from the historical controls is available. Where a valid historical control dataset was available, I used the mean tumor response in the controls to calculate the conditional probability of observing the trend seen in the study or a more significant trend if the true probability of response is the historical control average. Additionally, Dr. Corcoran references the manuscript by **Fung et al. (1996)**[4] as support for his approach to historical control analysis. However, one of the analysis methods used in the Fung article is similar to the one used in the Expert Report. This method has been shown to have sound and reliable statistical characteristics when there is no extra-binomial heterogeneity in the data and to be conservative when there is heterogeneity. For hemangiosarcomas, **Giknis and Clifford (2000)**[5] saw no tumors in 26 historical control studies (1,202 male CD-1 mice); there is no heterogeneity in these data. For kidney tumors, only the mean was provided for 46 historical control groups and only 11 animals out of 2,569 had a kidney tumor. This is broken down into seven adenomas seen in five studies and four adenocarcinomas seen in four studies; there is no heterogeneity in these data either. For the data presented here, the historical control test applied in the Expert Report was appropriate and methodologically sound. Any other reasonable statistical test applied to the four cases where historical controls changed a non-significant response to a significant response will yield effectively the same results.

IV. APPLYING LOGISTIC REGRESSION MODELING TO THE DATA SET

Dr. Corcoran criticized the pooled analysis of the data suggesting there should have been a correction for heterogeneity in the results. His long discussion of this issue, while perhaps relevant to epidemiology studies, would simply not work for animal carcinogenicity studies. In animal studies, one controls for all of the factors within a study that might make one exposure group different from any other. In pooling across multiple studies, I examined the individual experiments and only pooled data when it was clear the studies were close to identical. However, the approach suggested by Dr. Corcoran is also reasonable and it would be of value to see if the method of analysis suggested by Dr. Corcoran provides different results than the one used in the Expert Report. Thus, I reanalyzed the pooled data treating each experiment as a replicate while allowing for an effect of experiment in the evaluation (**Tables 2 and 3**). As suggested by Dr. Corcoran, the procedure used involved logistic regression modeling.

Table 2 shows four cases (highlighted in red) where the pooled analysis and the analysis using logistic regression differed in significance ($p<0.05$). In three of the four cases, the logistic regression provided a statistically significant finding where the pooled analysis was either marginal (two cases) or not significant (one case). For thyroid C-cell tumors in male Sprague-Dawley rats, the original significant finding is no longer supported and would suggest that the marginal statistically positive finding in **Lankas (1981)**[6] does not hold when compared to the other studies in the same sex and species and strain. In contrast, the lack of statistical significance for the pooled analyses of kidney adenomas and hepatocellular adenomas in male Sprague-Dawley rats and skin keratoacanthomas in male Wistar rats when combining **Brammer (2001)**[7] and **Wood et al. (2009)**[8] are reversed using logistic regression. This suggests a significant impact of glyphosate on the incidence of kidney adenomas and hepatocellular adenomas in male Sprague-Dawley rats and strengthens the finding of an increase in skin keratoacanthomas in male Wistar rats. Since kidney effects were also seen in the CD-1 mice, this strengthens the overall finding of an effect on kidney cancer rates in these animals. Since hepatocellular adenomas were also seen in Wistar rats, this strengthens that finding as well.

Four tumors in **Table 2** were not evaluated in the pooled analysis in the Expert Report; adrenal cortical carcinomas in female Sprague-Dawley rats and pituitary adenomas in male and female Wistar rats. These tumors did not appear in the Expert Report. Dr. Corcoran analyzed each of the individual tumor sites from all of the studies whereas the analysis in the Expert Report focused on tumors that were identified by regulatory authorities as increased in at least one study. Dr. Corcoran saw seven statistically significant tumor sites that were not discussed in the Expert Report. These are as follows: adrenal cortical carcinomas in female rats in the study by **Stout and Ruecker (1990)**[9]; skin intracutaneous cornifying epitheliomas (these are the same as keratoacanthomas) in male rats from the study by **Atkinson et al. (1993)**[10]; basal cell tumors in male rats in the study by **Enemoto (1997)**[11]; pituitary adenomas in both male and female rats in the study by **Wood et al. (2009)**[8]; splenic lymphosarcomas in female mice from the study by **Knezevich and Hogan (1983)**[2]; and Harderian gland adenomas in female mice from the study by **Sugimoto (1997)**[3]. In addition, after reviewing all of the findings in the Expert Report, it was

clear that the tumor incidence rates for skin keratoacanthomas in male rats from the study by **Enemoto (1997)**[11] were incorrect and an additional animal with this tumor was seen in the highest exposure group. Modifications to the original tables are provided as **Modified Tables 1-7** (rats) and **Modified Tables 9-12** (mice) in the Appendix. As before, where possible, any significant increase in a tumor as a function of dose seen in one study is analyzed in all remaining studies using the same sex, species, and strain. The new statistically significant findings are highlighted in the modified tables.

Returning to **Table 2**, after pooling all of the data for adrenal cortical carcinomas in female Sprague-Dawley rats, the exact trend test statistic is not significant. Logistic regression is also not significant with a p-value of 0.984. The lack of significance in this tumor is due to the high rates for this tumor in the **Lankas (1981)**[5] study and low rates in the remaining studies. The **Lankas (1981)**[5] study exposed rats for 26 months and the other three studies for only 24 months explaining, to some degree, the higher background rate in the **Lankas (1981)**[6] study (only six of the 25 cortical adenomas seen in this study occurred in rats dying before 730 days). Removing the **Lankas (1981)**[6] study and only pooling the three 24-month studies yields a significant trend in both tests. The significant trend seen for adrenal cortical adenomas cannot be easily discarded and suggest a potential for glyphosate to also affect adrenal cortical tumors.

For pituitary tumors in female Wistar rats, the pooled analysis was significant (p=0.005) and logistic regression was not significant (p=0.123). As noted in the Expert Report, the **Suresh (1996)**[12] study has very different control rates for pituitary tumors when compared with the other two studies. For this tumor, the categorical variable linked to the experiment by **Suresh (1996)**[12] was statistically significant (p<0.001). As before, if we remove the **Suresh (1996)**[12] study from the analysis and only pool the studies by **Brammer (2001)**[7] and **Wood et al. (2009)**[8], the results are statistically significant by both tests (**Table 2**). For pituitary tumors in male Wistar rats, none of the pooled analyses were significant (**Table 2**). These results would suggest there is limited support for an effect of glyphosate on pituitary adenomas in female Wistar rats.

Pooling the remaining new findings in Sprague-Dawley rats across the studies shows positive results for skin keratoacanthomas ($p_{pooling}$=0.010; $p_{logistic}$ =0.033) and basal cell tumors ($p_{pooling}$=0.011; $p_{logistic}$=0.020) in males. Since the pooled results for skin keratoacanthomas in male Wistar rats was also significant ($p_{pooling}$≤0.001; $p_{logistic}$ =0.008), there is strong support for an impact of glyphosate on skin keratoacanthomas in both male Sprague-Dawley rats and male Wistar rats.

Table 3 shows the pooled analyses for mice. None of the significant findings in the pooled analysis shown in the Expert Report were altered by the logistic regression analysis. For both hemangiosarcomas and kidney adenomas and carcinomas when pooling the 18-month studies by **Sugimoto (1997)**[3] and **Wood et al. (2009)**[3], the logistic regression model had difficulty

estimating the parameter for control response[1] so logistic regression was replaced with a simple linear model.

The Harderian gland adenomas seen in the study by **Sugimoto (1997)**[3] remain significant when combined with data from the other 18-month study by **Wood et al. (2009)**[13]. As seen in **Modified Table 11** (Appendix), there is a slight increase in Harderian gland tumors in the **Wood et al. (2009)**[13] study. The results remain statistically significant when combined with the results from **Knezevich and Hogan (1983)**[2]; **Atkinson (1993)**[10] did not evaluate Harderian glands.

The one remaining significant finding when applying logistic regression is an increase in composite lymphosarcomas in the spleen in female mice in the study by **Knezevich and Hogan (1983)**[2]. In the **International Classification of Diseases, Revision 9 (1975)**[14] (ICD-9), lymphosarcomas were classified under the heading of "Lymphosarcoma and reticulosarcoma". This was changed in **Revision 10 (1990)**[15] (ICD-10) where they are no longer classified[15]. In ICD-10, lymphosarcomas are approximately equal to lymphomas in the category of "Other specified types of non-Hodgkin lymphoma". This is a highly relevant finding for the causality argument for non-Hodgkin lymphoma in humans. This systemic tumor should be aggregated over all tissue sites with this tumor from this study. However, that is not possible without the individual animal pathology data from the study since, like malignant lymphomas, this tumor is aggressive and any animal with one tumor of this type is likely to have many other tumors of this same type; data summarized by organ cannot be used to obtain tumor incidence of at least one tumor in each animal. The remaining studies in CD-1 mice did not use this tumor classification for any of the lymphoid tumors identified; this is probably due to the classification change identified in ICD-10.

The new **Modified Table 15** (Appendix) includes all of the tumors identified in the Expert Report and those of Dr. Corcoran. In the original **Table 15**, when an increase occurred in both adenomas and in adenomas and carcinomas, only the more malignant finding was listed. In the **Modified Table 15**, that is no longer the case and each of these tumors is counted separately. With the exception of male Sprague-Dawley rats, the observed number of tumors are at or near the expected number for the different sex/strain groups in rats (**Modified Table 15**). For male Sprague-Dawley rats, 4.3 positive tumor findings with $p_{Trend} \leq 0.05$ or $p_{Hist} \leq 0.05$ are expected and 10 are observed (p=0.01) while 0.8 cases with $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ are expected and two were observed (p=0.21). In female CD-1 mice and Swiss Albino mice, the expected and observed numbers are approximately equal. However, in male CD-1 mice, there were 2.1 tumors expected for $p_{Trend} \leq 0.05$ or $p_{Hist} \leq 0.05$ and eight were observed (p<0.001) and there were 0.4 expected for $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ and five were observed (p<0.001). The findings

[1] In logistic regression, modeling is done using the logit(p) where p is the probability of response and modeling is done using $log\left(\frac{p}{1-p}\right) = \alpha + \beta \times dose$. If the control tumor response is 0, then $log\left(\frac{p}{1-p}\right) = -\infty$ and so the best estimate for α is also negative infinity. In these cases, numerical fitting algorithms have difficulty with estimating α which can effect the estimate and standard error of β. The general linear model has the form $p = \alpha + \beta \times dose$ and α can easily be estimated to be zero for the control response.

for male Sprague-Dawley rats and male CD-1 mice in these studies could not have occurred by chance alone. Even if one incorrectly groups all sexes and species together, there are 20.9 expected responses for $p_{Trend} \leq 0.05$ or $p_{Hist} \leq 0.05$ and 30 observed (p=0.032) and 4.2 expected responses for $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ and 12 observed (p=0.001). Thus, chance does not explain all of the positive results seen in these studies.

Dr. Corcoran makes only one comment relating to **Table 15** suggesting that the historical control evaluations explain the difference between **Table 15** and his results. As noted earlier, the use of historical control data in this instance is justified and based on sound and accepted methodology given the rarity of the four tumor sites where the historical control data made a difference. If the historical control evaluations are included in **Modified Table 15**, that adds three additional evaluations to the male rats (one with p<0.01), 1 to female rats (p<0.001), 0 to female mice and 18 to male mice (five with p<0.01 and eight with p<0.05). The number of evaluations for each group would then become 22 for male rats, no real change for female rats or female mice, and a change to 13.5 for male mice. The number of findings in the **Modified Table 15** that were significant at p≤0.05 by either test would change from 30 (expected 20.9) out of 418 reasonable analyses (p=0.032) to 38 (expected 22) out of 440 (p<0.001). Similarly, the number of findings in the **Modified Table 15** that were significant at p≤0.01 by either test would change from 12 (expected 4.2) out of 418 reasonable analyses (p=0.001) to 18 (expected 4.4) out of 440 (p<0.001). It is clear that incorporation of the tests using historical controls into **Modified Table 15** would make it even less likely that all of these findings are due to chance.

V. CONCLUSION

Dr. Corcoran has raised certain issues relating to the pooling of experiments that have been addressed in this response. There is no significant difference between the results from the methods proposed by Dr. Corcoran and those in the Expert Report. Both are sound methods for evaluating the overall significance of multiple animal carcinogenicity studies. Dr. Corcoran also identified several tumors that were not evaluated in the Expert Report, which are now included in my expert opinion as updated in this response. Dr. Corcoran also expressed concerns about the number of analyses and the effect of all of these analyses on false-positive error rates. As explained above, Dr. Corcoran misunderstood how analyses are conducted for animal cancer studies.

In summary, Dr. Corcoran's concerns have led to additional analyses that strengthen the case that glyphosate causes cancers in rodents, especially lymphatic and hematological cancers in male mice. The new analyses strengthen the biological plausibility, biological gradient, and coherence arguments developed by **Hill (1965)**[16] supporting the conclusion that glyphosate can cause non-Hodgkin lymphoma in humans.

Table 1: Number of tumor sites with one, two, and three or more tumors in all dose groups combined from the 12 rodent studies of glyphosate

Study	Numbers of Sites with Specified Number of Tumors in All Exposure Groups					
	Exactly 1 Tumor		Exactly 2 Tumors		3 or More Tumors	
	Males	Females	Males	Females	Males	Females
Lankas (1981) S-D Rats	16	17	4	2	22	25
Stout and Ruecker (1990) S-D Rats	21	24	7	4	16	12
Atkinson et al. (1993) S-D Rats	20	16	5	3	15	9
Brammer (2001) Wistar Rats	20	20	5	5	16	13
Suresh (1996) Wistar Rats	17	20	2	3	11	9
Enemoto (1997) S-D Rats	29	18	3	5	21	12
Wood et al. (2009) Wistar Rats	27	17	2	8	19	14
Totals Rats	150	132	28	30	120	94
Average Rats	21.5	18.9	4	4.3	17.1	13.4
Knezevich and Hogan (1983) CD-1 Mice	20	44	5	7	9	17
Atkinson et al. (1993) CD-1 Mice	10	11	4	2	9	14
Wood et al. (2009) CD-1 Mice	8	14	2	2	10	13
Sugimoto (1997) CD-1 Mice	10	14	5	5	6	11
Kumar (2001) Swiss Albino Mice	4	16	3	2	8	8
Total Mice	52	99	19	18	42	63
Average Mice	10.4	19.8	3.8	3.6	8.4	12.6

Table 2: Comparison of pooled analyses with and without a correction for experiment in Rats

Studies	Sex	Tumor	General Linear Model		Original Pooled Analysis
			Slope (se)	P-value	
Lankas (1981)[6] Enemoto (1997)[11] Atkinson et al. (1993)[10] Stout and Ruecker (1990)[9] Sprague-Dawley Rats	M	Testicular Interstitial Cell Tumors	0.513 (0.517)	0.461	0.608
	F	Thyroid C-cell Adenomas and Carcinomas[2]	2.95 (2.79)	0.145	0.390
	M	Thyroid C-cell Adenomas and Carcinomas	2.29 (2.78)	0.205	0.041
	M	Thyroid Follicular-cell Adenomas and Carcinomas[2]	0.930 (5.49)	0.433	0.618
	M	Pancreas Islet-Cell Tumors[2]	3.02 (4.07)	0.260	0.275
	M	Hepatocellular Adenomas[2]	9.65 (4.30)	0.012	0.073
	M	Kidney Adenomas[2]	14.3 (8.27)	0.042	0.200
	M	Kidney Adenomas (excluding Lankas, 1981)	14.7 (8.29)	0.038	0.031
	F	Adrenal Cortical Carcinoma[2]	26.5 (13.6)	0.984	0.997
	M	Skin Keratoacanthoma	11.1 (4.61)	<0.001	<0.001
	M	Basal Cell Tumors	23.3 (11.4)	0.020	0.011
Brammer (2001)[7] Wood (2009)[8] Suresh (1996)[12] Wistar Rats	M	Hepatocellular Adenomas[2]	40.0 (20.9)	0.030	0.051
	F	Mammary Gland Adenomas and Adenocarcinomas[2]	2.11 (3.25)	0.258	0.459
	M	Skin Keratoacanthoma[2]	10.4 (5.65)	0.033	0.010
	M	Pituitary Adenomas[2]	0.266 (2.32)	0.454	0.177
	F	Pituitary Adenomas[2]	1.89 (1.64)	0.123	0.005
Brammer (2001)[7] Wood (2009)[8] Wistar Rats	M	Hepatocellular Adenomas	1.32 (6.11)	0.015	0.013
	F	Mammary Gland Adenomas and Adenocarcinomas[2]	7.00 (3.62)	0.027	0.037
	M	Skin Keratoacanthoma[2]	10.4 (5.65)	0.033	0.053
	M	Pituitary Adenomas	0.146 (2.38)	0.476	0.503
	F	Pituitary Adenomas[2]	3.34 (1.76)	0.029	0.017

Entry is multiplied by 10^4 for ease in presentation; [2]at least one of the categorical variables for experiment in the logistic regression analysis for these tumors was statistically significant ($p<0.05$)

Table 3: Comparison of pooled analyses with and without a correction for experiment in CD-1 Mice

Studies	Sex	Tumor	General Linear Model		Original Pooled Analysis
			Slope (se)	P-value	
Sugimoto 1997[3], Wood 2009[13] 18 Month	M	Hemangiosarcoma[1]	7.91e-2 (1.81e-7)	<0.001	0.015
	M	Kidney Adenoma and Carcinoma[1]	7.91e-2 (1.81e-7)	<0.001	0.015
	M	Malignant Lymphoma	4.24 (1.67)	0.005	0.005
	M	Lung Adenocarcinoma[2]	2.24 (1.47)	0.063	0.417
	F	Hemangioma (any tissue)	5.92 (2.293)	0.005	<0.001
	F	Harderian Gland Adenoma	3.66 (1.81)	0.021	0.005
Atkinson 1993[17], Knezevich 1983[2] 24 Month	M	Hemangiosarcoma	3.58 (4.32)	0.204	0.490
	M	Kidney Adenoma and Carcinoma	2.89 (2.00)	0.075	0.081
	M	Malignant Lymphoma	-0.739 (1.53)	0.686	0.653
	M	Lung Adenocarcinoma[2]	-2.28 (2.01)	0.872	0.985
	F	Hemangioma (any tissue)	-3.62 (5.88)	0.731	0.424
Sugimoto 1997[3], Wood 2009[13], Atkinson 1993[17], Knezevich 1983[2]	M	Hemangiosarcoma[2]	6.82 (3.72)	0.033	0.045
	M	Kidney Adenoma and Carcinoma	4.12 (1.84)	0.013	0.005
	M	Malignant Lymphoma	1.36 (1.02)	0.093	0.073
	M	Lung Adenocarcinoma[2]	0.259 (1.10)	0.407	0.937
	F	Hemangioma (any tissue)	3.01 (1.61)	0.031	0.018
	F	Harderian Gland Adenoma[2,3]	2.77 (1.62)	0.043	0.005

Entry is multiplied by 10^4 for ease in presentation; [1]because this tumor had a zero response in the control and low exposure groups and because the logit(0)=-infinity, the logistic regression was not appropriate in this case and a simple general linear model was used; [2]at least one of the categorical variables for experiment in the logistic regression analysis for these tumors was statistically significant ($p<0.05$); [3] this analysis excludes the study by Atkinson et al. (1993) since they did not examine Harderian gland

REBUTTAL OF DR. FOSTER

I. INTRODUCTION

Dr. Foster dismissed 18 of the 19 statistically significant findings in the animal carcinogenicity studies identified in my Expert Report. He did not comment on the increased incidence of hemangiomas in female Swiss albino mice in the study by Kumar (2001)[18]. Dr. Foster provided rationale for each of his dismissals based on the significant changes in tumor incidence failing to meet his criteria for a positive study. Table 4, illustrates the six categories of criteria that Dr. Foster uses to dismiss statistically significant ($p \leq 0.05$) positive findings from the 12 studies exposing rats and mice to glyphosate. Only certain categories were relevant to any one positive finding discussed in the Expert Report. The categories used by Dr. Foster are briefly described below:

Dose-Response: For several tumors, Dr. Foster, as one of his arguments, found there was no dose-response in the data.

Historical Control: Failure of the response to be outside the range of the historical control data or for the control response to be below the range of the historical control data was also an argument Dr. Foster used to dismiss studies.

Precursor Lesion: Some tumors can go through a progression from non-malignant lesions to cancer; failure to see increases in both non-malignant tumors and malignant tumors was another criterion Dr. Foster used.

Other Studies: If all of the studies did not give the same result, Dr. Foster used this as part of the criteria for dismissal.

Survival: In two studies, survival in the highest exposure group was different than in the controls, and Dr. Foster used this as part of the reason for dismissal.

Fisher Test: In several studies, Dr. Foster used a lack of statistically significant pairwise comparisons between the higher doses and controls as part of the reasoning to dismiss positive tumor findings.

Rather than going study-by-study and addressing these points, this rebuttal looks at each category separately and then discusses their impact in each study.

II. Dose-Response

Dr. Foster shows a lack of understanding of statistics in the use of this criteria. While Dr. Foster does not define what he means by a lack of dose-response, my interpretation of this concept is that as the dose increases, the probability of a tumor cannot decrease (this is known as a non-decreasing function in mathematics). As an example, if the responses from control to high dose

in a four-dose study were 2%, 3%, 5%, 7%, this would constitute clear dose-response whereas 2%, 1%, 4%, 7% would not. The problem with this criterion is that it has very significant impacts on false-positive and false-negative rates.

In any statistical analysis, there is a null hypothesis and an alternative hypothesis. In an animal carcinogenesis study, the null hypothesis means there is no impact of the chemical on the tumor rates; the alternative hypothesis means the chemical increases the tumor rates. A false-positive error occurs when one incorrectly rejects the null hypothesis and decides the chemical causes cancer when it really does not cause cancer. A false-negative error occurs when one does not reject the null hypothesis even though the chemical does cause cancer. The rates at which these errors occur for a specific test can be calculated.

So, what is the impact of requiring non-decreasing dose-response in addition to statistical significance? Using statistical simulations[2], it is easy to answer this question. Consider one of the examples where dose-response was part of Dr. Foster's criteria for dismissing the tumor. In the study by **Sugimoto (1997)**[3], the control response for malignant lymphomas in male CD-1 mice was 4% and the response in the high exposure group was 12%. Let's begin by estimating the probability of a false-positive error and the impact of requiring non-decreasing dose-response.

If we assume that the true background is 4% and there is no dose-response, then we can, by random sampling on the computer, generate 1,000 datasets where each group is assumed to have a true response of 4% regardless of the dose. By random chance, these groups will sometimes result in a positive response. If we reject the null hypothesis when $p_{Trend} \leq 0.05$, the exact trend test yields a false positive rate of 5%. That is, 5% of the time, by chance, the null hypothesis will be rejected. This is exactly what should happen when a test is operating correctly. What happens then if we also require that the resulting pattern of dose-response be non-decreasing? Using the exact same simulated data, the resulting false-positive error rate now drops to 2.8%, almost half of what was expected. On the surface, one might think this is a good and acceptable outcome since the error rate has dropped, but by reducing the false-positive rate, the false-negative rate increases. Let's again look at our example.

[2] Statistical simulations are a critical tool for understanding the behavior of a statistical test in a specific setting. In this case, 1000 samples are draw from a binomial distribution where the underlying probability of a tumor and the number of animals is specified; for example, the probability of a tumor is 0.04 for all of the groups when calculating the probability of a false positive error and each dose group has 50 animals in it. For each simulated data set produced, the Armitage linear trend test is applied and if the p-value is ≤0.05, that simulation is given a value of 1 (positive tumor trend with increasing exposure) otherwise, it is given a value of zero. After 1000 simulations are completed, the number of cases with a value of 1 are counted and the estimated false-positive error rate is that number divided by 1000. Thus, for the case discussed above, fifty of the 1000 simulations were assigned a value of 1 and the underlying false-positive error rate is then 50/1000=0.05 or 5%.

Table 4: Criteria used by Dr. Foster to dismiss 19 statistically significant (p≤0.05) identified using the Armitage linear trend test in proportions to evaluate 12 studies of glyphosate exposure to rats and mice

Study	Sex	Tumor	Dose-Response	Hist. Cont.	Pre-Cursor Lesion	Other Studies	Survival	Fisher Test
Lankas (1981) SD Rat	M	Testicular Tumors	x	x	x	x	x	
	F	Thyroid C-Cell			x	x		
Stout and Ruecker (1999) SD Rat	M	Liver Adenomas	x	x	x	x		
	M	Liver Adenomas and Carcinomas	x	X	x	x		
	F	Kerato-acanthoma (p>0.05)		x				
	F	Thyroid C-Cell Adenomas		x				
	F	Thyroid C-Cell Adenomas and Carcinomas		x				
Brammer (2001) Wistar Rats	M	Liver Adenomas	x	x	x		x	
Wood et al. (2009) Wistar Rats	F	Mamm. Gland Adeno-carcinomas	x	x		x		
	F	Mamm. Gland Tumors	x	x		x		
	M	Kerato-acanthoma	x					x
Atkinson et al. (1993) SD Rats	M	Follicular Cell Tumors		x		x		
Enemoto (1997) SD Rats	M	Kidney Adenomas	x		x	x		x
Knezevich and Hogan (1983) CD-1 Mice	M	Kidney Tumors	x		x	x		
Atkinson (1993)	M	Hemangio-sarcoma		x		x		
Sugimoto (1997)	M	Malignant Lymphoma	x	x		x		x
	F	Hemangiomas				x		
Wood et al. (2009)	M	Malignant Lymphomas		x				
	M	Lung Adeno-carcinoma	x		x	x		x

Now, instead of assuming there is no dose-response, assume there is linear dose-response with the response in the control group is 4% and the response in the high exposure group is 12%. Since this response is linear with dose, and we use the doses for males from the **Sugimoto (1997)**[3] study, the expected response at the four dose groups are 4% at control, 4.3% at 165 mg/kg, 5.5% at 838.1 mg/kg and 12% at 4348 mg/kg. Using these as the target responses at each dose, 1,000 studies with random error can be simulated and one can count how often the null hypothesis is not rejected and an incorrect conclusion that the chemical does not cause malignant lymphomas is accepted. Using only the trend test, without the requirement of non-decreasing dose-response, yields a false-positive error rate of 29%. This is not a bad rate for this shallow dose-response. Requiring that the dose-response be non-decreasing results in a false-positive error rate of 86%. This is unacceptable and is not surprising. Just evaluating response at control and at the lowest dose, one can see that they are almost identical in response. Thus, by random chance, one would expect the lowest dose to be below the control response about 50% of the time and each time this happens, Dr. Foster's approach would reject any positive finding in a trend test. Thus, regardless of the responses in the other exposure groups, one would accept the null hypothesis and generate a false-negative error.

Dr. Foster used this argument as one of his reasons for dismissing 11 of the 19 tumors (58%) with significant dose-response trends. His use of these criteria is not methodologically sound.

III. Historical Controls

Dr. Foster begins his discussion of the interpretation of the bioassay results by stating "*I agree with Dr. Portier that it is best to compare data with contemporary controls*". Despite this statement, Dr. Foster then goes on to use historical controls as part of his reasons for dismissing 13 of the 19 tumors (68%) in Table 4. In simple terms, rejecting a significant finding observed when comparisons are made to the concurrent control because the responses fall into the range of the historical controls is akin to replacing the concurrent control with the largest control response ever seen.

During the course of an animal study, all aspects of the animal's life are controlled; the air they breathe, the food they eat, the light-dark cycle in the laboratory, handling of the animals, etc. Certain issues are very difficult to control such as noise in the laboratory, outside radiation that may seep into the laboratory, slight differences in batches of feed from one week to the next, odors drifting in from other areas of the building, etc. For these uncontrolled variables, every animal in the study is subject to the same problems, thus the controls in the study see the same uncontrolled exposures as do the treated animals. In addition, while strains of animals may be the same, there is variability in response if the animals arise from different laboratories or are even born at different times of the year. When controls are used from another study, this allows for the possibility that uncontrolled factors from that other study could have affected those controls making their response different from the concurrent control and from the animals exposed in the current experiment. Most of the guidelines developed for animal studies clearly state that the concurrent control is the best control to use for analyzing a cancer

bioassay as noted on page 21 of the Expert Report. In fact, the IARC guidelines[19] are explicit on the issue of using historical controls stating that

> "*Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability.* ***It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls****, particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals*" (emphasis added).

The scientific reasons for not using historical control ranges to reject a positive finding are clear, but there is also a statistical reason. As the number of studies in the historical control database increases, so does the range of responses. The net effect of this is that, as the historical control dataset gets larger, one is more likely to reject a positive if one insists the response be outside the range of the historical controls. Again, going back to the example of malignant lymphomas in male mice from the study by **Sugimoto (1997)**[3], the false positive rate is 5% when only the exact trend test is applied to the simulated data where there are no chemical-related effects in any of the dose groups. If there are 10 historical control groups with exactly the same background response as the controls (4%) and no extra-binomial variability (which could be caused by uncontrolled or different exposures), the false-positive error rate drops to 1.9% and if there are 26 historical control groups, as is the case for the **Sugimoto (1997)**[3] study, the false-positive error rate drops to 1.1%. This results in an increase in the false-negative error rate from 29% using just the trend test results to 38% with 10 historical control groups to 50% for 30 historical control groups.

This increase in the false-negative rate is expected since one is only rejecting positive findings, never rejecting negative findings.

Dr. Foster's discussion regarding the range of the historical control data is misleading. Again, consider the example of malignant lymphomas in male rats from the study by **Sugimoto (1997)**[3]. Dr. Foster concludes "*… the incidence of these tumors falls within the range of historical controls in the Giknis (2000) report (0-14%) cited by Dr. Portier and the range of historical controls (3-19%) from contemporaneous studies conducted at the same laboratory (BFR, 2015)".* After studying the **BfR (2015)**[20] document, I can only find one reference to

historical controls for malignant lymphomas in male Wistar rats (page 91) which references the study by **Giknis and Clifford (2000)**[5], showing a range of 1.45% to 21.7%. However, they misread the **Giknis and Clifford (2000)**[5] paper, grouping 18-month controls with 24-month controls and failing to recognize there were 13 studies with no tumors in the controls making the lower range value 0%.

Figure 1 shows a histogram of the incidence rates in the twenty-six 18-month historical control groups for malignant lymphomas in male CD-1 mice from the study by **Giknis and Clifford (2000)**[5]. It is clear from this figure that the control response from the study by **Sugimoto (1997)**[3] is easily within the usual range of control responses for malignant lymphomas in male Wistar rats. The higher end of the historical control is driven by response in a single study that is almost double the value of the next lowest response and about five times the value of the median response. This pattern is quite common in the tumors that Dr. Foster dismisses because of historical controls. This is demonstrated by the five examples presented in **Figure 2**. In all five cases, the control tumor response is in a reasonable range of the historical control response and there is good reason to use the concurrent control group in the analysis and ignore the historical controls.

Figure 1: Incidence rates in the twenty-six 18-month historical control groups for malignant lymphomas in male CD-1 mice from the study by **Giknis and Clifford (2000)**[1]

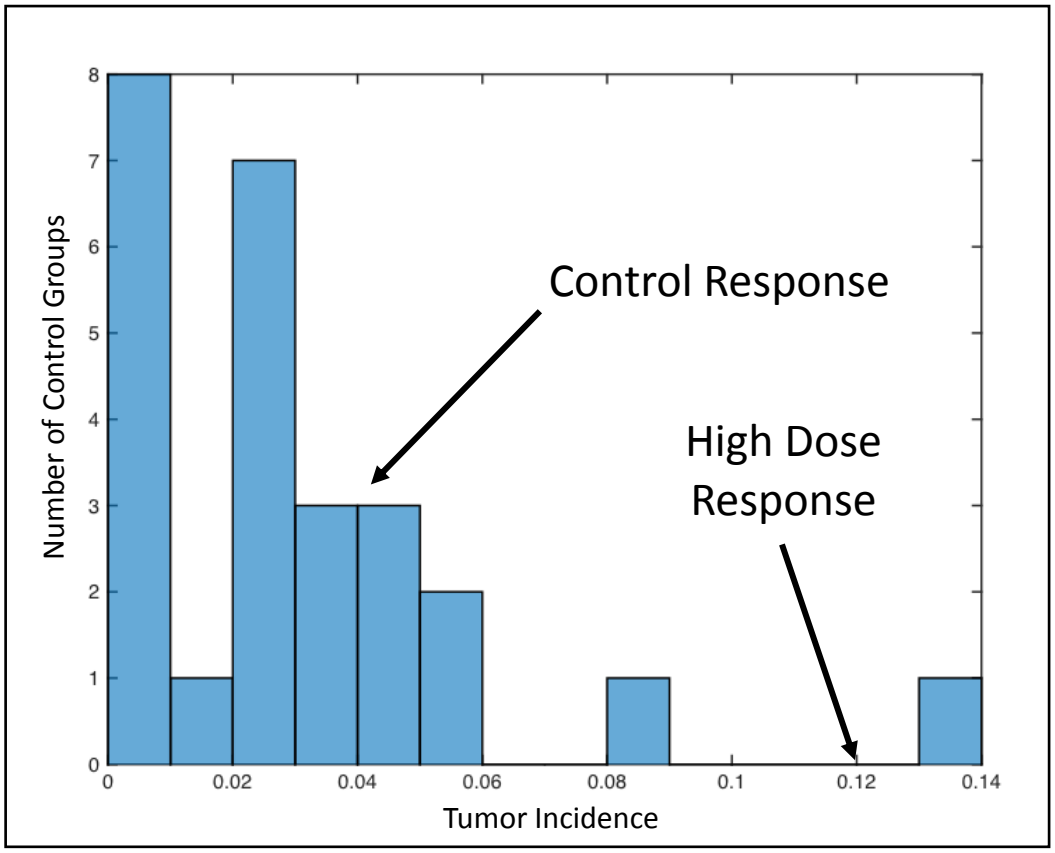
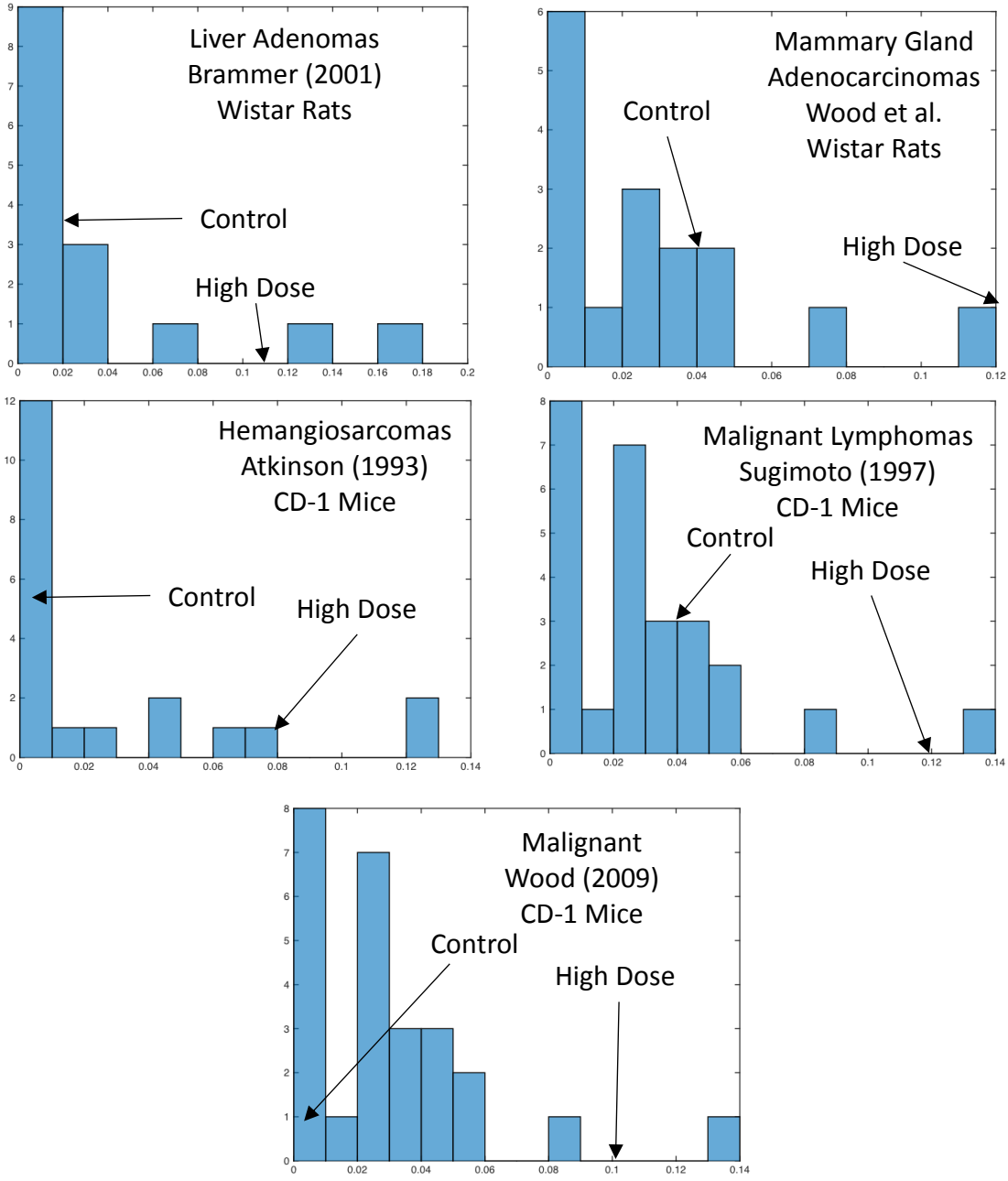


Figure 2: Incidence rates in the historical control groups for several tumors



Dr. Foster is also very selective in his presentation of the historical control data, not mentioning situations where the tumor response is well outside the range of the historical controls. Here are two examples:

Lankas (1981)[6]: Testes interstitial cell tumor – historical control range 3-7% (Monsanto), 0% to 9.3% (**Giknis and Clifford (2004)**[21]) – response at highest dose is 12%

Enemoto (1997)[11]: Kidney Adenoma – historical control range 0%-4% (**Giknis and Clifford (2011)**[22]), note 23 of 30 studies had 0% in the control group) – response at highest dose is 8%.

There were several other wrong or misleading comments in Dr. Foster's report regarding historical controls. On page 18, he mentions the average historical control rate of mammary gland tumors in female Sprague-Dawley rats (57%) and in the same sentence includes Wistar rats implying the control rate of mammary gland tumors in these animals is also large. However, according to **Giknis and Clifford (2011)**[22] the mean response for mammary gland adenomas in female Wistar rats is 2.22% and for adenocarcinomas it is 2.96%. He also states on page 24 that the historical control data from **Giknis and Clifford (2005)**[23] "*indicate it is unusual to have zero lymphomas in the control group*" of male Wistar rats. However, **Giknis and Clifford (2005)**[23] show 8 of the 26 control groups (31%) from 18-month studies have no animals with a malignant lymphoma; thus having no tumors in the control group is not unusual. The actual responses for malignant lymphomas for all of the control groups in the database provided by **Giknis and Clifford (2005)**[23] are shown in **Figure** 2.

Finally, there are four tumor sites where, used correctly, the historical control data does contribute to the interpretation of the result. These four are kidney carcinomas (p_{Trend}=0.063, p_{Hist}=0.002) and adenomas and carcinomas (p_{Trend}=0.065, p_{Hist}=0.011) in the study by **Knezevich and Hogan (1983)**[2], and kidney adenomas (p_{Trend}=0.062, p_{Hist}=0.005) and hemangiosarcomas (p_{Trend}=0.062, p_{Hist}=0.004) in the **Sugimoto (1997)**[3] study. For hemangiosarcomas, **Giknis and Clifford (2000)**[5] saw no tumors in 26 historical 18-month control studies (1,202 male CD-1 mice) making the two tumors seen in the highest dose group in the study by **Sugimoto (1997)**[3] both statistically and biologically compelling. For kidney tumors, **Giknis and Clifford (2000)**[5] only provide the mean tumor response for 46 historical control groups (twenty-six 18-month studies and twenty 24-month studies) and only 11 animals out of 2569 (0.4%) had a kidney tumor. This is broken down into seven adenomas seen in five studies and four adenocarcinomas seen in four studies; thus 41 control groups had no adenomas and 42 had no adenocarcinomas with the remaining four groups each having only one adenocarcinoma. Thus, the two adenomas seen in the study by **Sugimoto (1997)**[3] and the three carcinomas seen in the study by **Knezevich and Hogan (1983)**[2] are significant and biologically important.

Thus, Dr. Foster provides an unbalanced evaluation of the historical control data, failing to discuss it when it strengthens a significant finding and incorrectly using the range of the historical controls to reject the concurrent control group.

IV. Precursor Lesions

Dr. Foster seems to believe that virtually all tumors arise from precursor lesions like hyperplasia and adenomas and that if one does not see increases in both adenomas and carcinomas, the finding is not chemically related and can be dismissed. This is an overly simplistic view of a complicated process. For example, if one looks at human digestive tract cancers, while it is clear that many carcinomas arise from adenomas, it is also likely that some arise *de novo*[24-26].

In humans, other organs and tissues have not been as carefully studied. In animal studies, there are numerous cases in which carcinomas and adenomas combined are increased when adenomas are not increased, many cases where adenomas are increased without an increase in carcinomas and fewer cases where only carcinomas are increased. For example, in an evaluation[27] of 64 National Toxicology Program (NTP) carcinogenicity studies in rats and/or mice that produced alveolar/bronchiolar adenomas and/or carcinomas, there are multiple studies that the NTP labels as clear evidence of carcinogenicity or positive for carcinogenicity[3] where there are only adenomas, only carcinomas or both.

Cancer is a multistage process which changes cells from being normal to being malignant through a variety of steps (**Figure 3**). In general, normal cells obtain damage to their DNA. Normally, this damage can be repaired by processes in the cell that specialize in keeping the DNA sequence from changing. If the damage to the DNA is not repaired and the cell replicates, the change in the DNA sequence can become permanent in the cell and is referred to as a mutation. Most cancers require cells to undergo several mutations before the cell will completely lose growth control and begin invading the surrounding tissue. Chemicals can affect this process at many points as cells progress from a normal state to a malignant state (**Figure 3**). Precursor lesions, like hyperplastic nodules and adenomas, are generally thought to be derived from cells that are at early stages of the carcinogenic process.

Two issues are critical in understanding what is seen in the results of an animal bioassay versus the underlying biology. First, all tumors in a glyphosate study are only observed at one time in the course of the study; when the animal dies. Thus, this entire process of multistage carcinogenesis is invisible because one does not see the adenoma in the animal and then later see the carcinoma; one only sees some animals with adenomas and others with carcinomas. Second, seldom will pathologists examine the tissue surrounding a tumor and list an animal as having both a carcinoma and an adenoma. Since carcinomas generally grow faster than adenomas, the carcinoma would be the predominant pathology and that animal would be listed as having only the carcinoma. Hence, there is a likely under-reporting of the potential number of adenomas that actually occurred.

If a chemical affects mutations or cellular replication at an early stage in this process and the final stages in the process occur spontaneously (without chemical impact), one is likely to see an increase in all of the precursor lesions as well as malignancies. As an example, suppose a chemical increases the probability of having an adenoma from 10% to 30% and the probability of an adenoma becoming a carcinoma remains constant at 30%; then, with 50 animals in each group, you would expect five adenomas in controls and 15 in the treated animals. If 30% of these adenomas progress to become malignancies, one would expect one to two animals with carcinomas in controls and four to five carcinomas in the exposed animals. Now, because the carcinoma would grow within the adenoma, one is no longer likely to count an animal with a carcinoma as having an adenoma because the cancer becomes the predominant pathology. Thus, one would likely see adenomas in three to four animals (subtract one to two from the

[3] Clear evidence and positive are designations used by the National Toxicology Program for chemicals that causally induced the observed increase in tumors.

original five) in control and nine to 10 animals in the treated group (subtract five to six from the original 15).

If the tumor affects all stages of the process, then other patterns can occur. Consider the same example, but the chemical changes the rate at which adenomas become carcinomas from 20% to 60%. Now, one would expect one to two animals with carcinomas in the controls and nine animals in the treated group. The number of expected adenomas would then be three to four in controls and drop to six in the high dose group, an increase that is not likely to be significant.

If the chemical only affects the late stages (not the early stages) of cancer development, an actual decrease is seen in the adenoma counts. For example, if adenomas occur spontaneously in 30% of the animals, then with 50 animals in each group, it is expected that 15 animals in both the control and treated groups will develop adenomas. If the chemical changes the rate of conversion from adenomas to carcinomas from 20% to 60%, one would expect three tumors in the control group and nine in the treated group. Subtracting these from the adenoma counts would result in adenomas in 12 control animals and only six treated animals; a decrease.

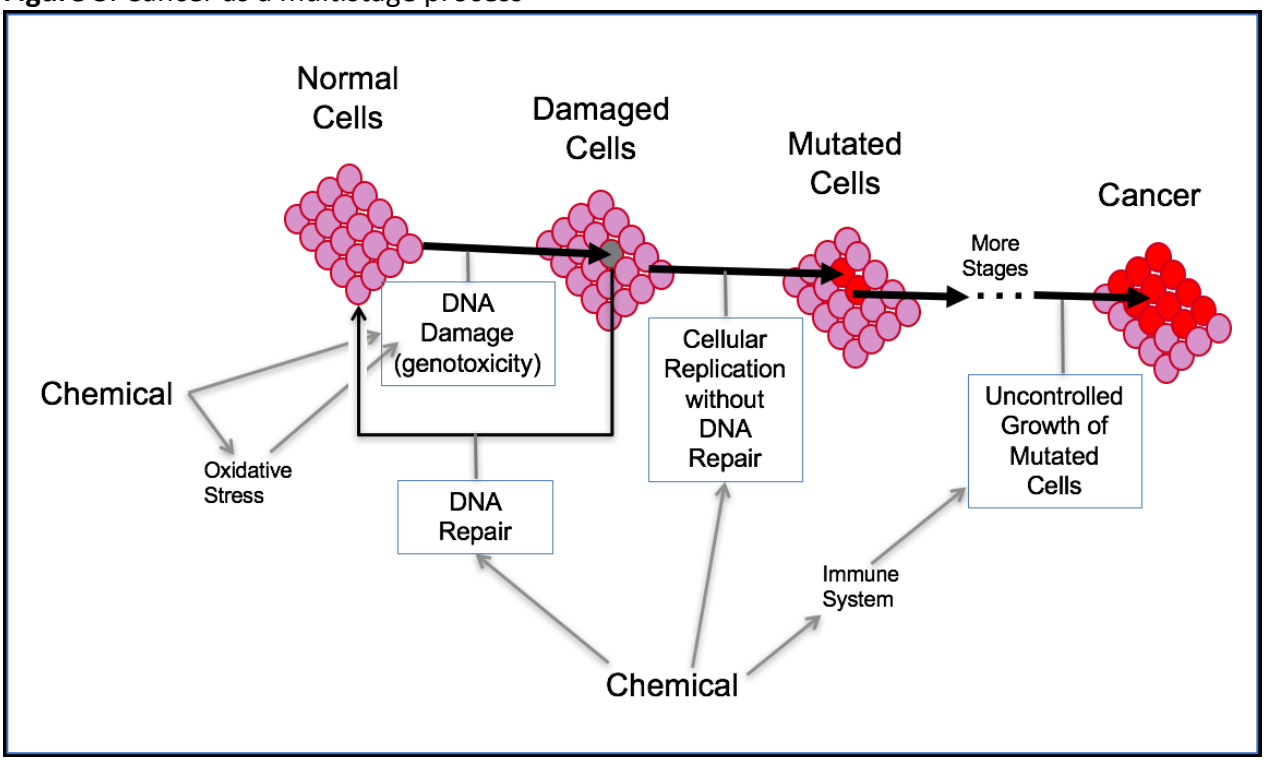
Time also plays a role in this process. Even if the chemical is affecting all stages of the process, the final stages of tumor progression may take longer than the animal lives, resulting in an increase in adenomas without a subsequent increase in carcinomas.

Finally, genotoxic carcinogens have the capability to produce carcinomas without adenomas through rapidly inducing multiple mutations. Along these same lines, some tumors have no precursor lesions (e.g. malignant lymphomas, hemangiosarcomas)

While this is a simplistic illustration of a very complicated process, it outlines the basic reasons why any pattern is possible when one is only evaluating tumors in the animals at one point in time and counting adenomas and carcinomas.

As an illustration using real data, consider the lung adenomas and adenocarcinomas seen in male mice in the study by **Wood et al. (2009)**[13]. Going from control to highest dose, adenoma counts were 9/51, 7/51, 9/51 and 4/51 while adenocarcinoma counts were 5/51, 5/51, 7/51 and 11/51. In not one case is there an animal listed with both of these pathologies in the lung. Unless Dr. Foster is arguing that the pathological diagnoses are wrong, this could clearly be a case where glyphosate is affecting the late stages of carcinogenesis resulting in a movement of tumors from adenomas to adenocarcinomas without increasing the incidence of the combined tumors. Looking at hepatocellular adenomas and carcinomas in males in that same study, the rates for adenomas are 1/51, 1/51, 4/51 and 2/51 while the counts for carcinomas are 6/51, 11/51, 7/51 and 4/51. Again, there were no animals with both adenomas and carcinomas and in every group, the carcinoma counts exceed the adenoma counts suggesting either carcinomas do not arise from adenomas or that adenomas are rapidly converted to carcinomas.

Figure 3: Cancer as a multistage process



V. Other Studies

Dr. Foster argues to dismiss 13 of the 19 tumors (68%) in Table 4 because the same tumor was not seen in other studies of the same sex and species. This is again a misinterpretation of what a statistical p-value means when applied to an animal carcinogenicity study. As an illustration of why this strategy could be very misleading, consider the case of four animal cancer studies where the p-values for an increase in malignant lymphomas are 0.01, 0.051, 0.051 and 0.051. This means that there is only a 1%, 5.1%, 5.1% and 5.1% chance that the null hypothesis (the chemical does not increase the cancer risk) is true. On the other hand, if the p-values would have been 0.01, 0.05, 0.05 and 0.05, Dr. Foster would then say they all gave the same answer. Reaching these two different opinions based on a difference of 0.1% in p-values does not properly portray the importance of the results. In the first case, converting the results from multiple bioassays into yes or no decisions and then concluding there is no cancer hazard if all the studies are not a yes ignores the fact that all of the studies are telling us there is a consistent increase with exposure in these hypothetical data. The entire purpose of the pooled analysis is to objectively address this question rather than merely counting positive versus negative studies. As an example, consider lung adenocarcinomas in females in the two 18-month studies in CD-1 mice. **Wood et al. (2009)** has a p-value of 0.028 whereas **Sugimoto (1997)** has a p-value of 0.148. Combined, the overall p-value is not significant (p=0.484) suggesting there is no effect and, in this case, I would agree with Dr. Foster. On the other hand, hemangiomas in female mice in the same two studies have p-values of 0.002 and 0.438 with the combined analysis having a p-value of 0.001; in this case, I disagree with Dr. Foster that a

positive finding and a negative finding results in a negative finding. The presumption that there is no cancer hazard whenever two or more carcinogenicity studies differ in the statistical significance of a particular tumor site is scientifically unsound and should not be used as a reason for ignoring positive findings.

VI. Survival

For two of the tumor findings, Dr. Foster argues that survival differences could allow animals in the high-dose group to live longer and could explain the significant tumor increases. The EPA disagrees with Dr. Foster regarding survival differences in the study by **Lankas (1981)**[6]. To be even more rigorous in my analysis, I used the poly-3 test adjustment for survival differences[28, 29] and reanalyzed the data. This test is similar to the Armitage linear trend test but adjusts the number of animals at risk of getting the tumor based upon duration of life and is commonly used to analyze bioassays by the US National Toxicology Program. Testicular tumors in male Sprague-Dawley rats from the **Lankas (1981)**[6] study had a p-value without survival adjustment of p_{trend}=0.009 and with survival adjustment of p_{trend}=0.015. Dr. Foster's comments regarding survival differences for hepatocellular adenomas in male rats in the study by **Brammer (2001)**[7] cannot be resolved since individual animal times of death and tumor status are not publicly available and these data were not provided by Monsanto. In essence, this is not an issue.

VI. Fisher's Test

For four tumors, Dr. Foster uses, as part of his argument for dismissal, the observation that the pairwise comparisons via Fisher's exact test were not significant even though the trend test findings were. As noted on page 20 of the Expert Report, virtually all regulatory bodies consider a positive finding in either test as sufficient evidence to reject chance as leading to the positive finding.

VIII. Summary

Dr. Foster's methods for evaluating and drawing conclusions from animal carcinogenicity studies suffers from a lack of understanding in and/or experience with statistics, a failure to understand the correct role of historical controls, a dogmatic view of adenomas and carcinomas that is not supported by either scientific theory or data, a failure to properly evaluate the same findings over multiple studies, and a lack of understanding of findings from pairwise versus trend analyses. Dr. Foster's comments do not impact my conclusion that the animal data provide strong evidence for the biological plausibility, biological gradient, and coherence arguments developed by **Hill (1965)**[16] supporting the conclusion that glyphosate can cause non-Hodgkin lymphoma in humans.

In this Rebuttal Report, I have not provided comments on the remaining five expert reports (Dr.s Fleming, Goodman, Mucci, Rider, and Rosol) provided by Monsanto. My lack of comments on these reports does not constitute acceptance of the arguments in these reports.

It is still my opinion that glyphosate probably causes NHL based on the human, animal and experimental evidence and that, to a reasonable decree of scientific certainty, the probability that glyphosate causes NHL is high. Nothing in the reports submitted by Monsanto, including the two reports that I respond to in this rebuttal report, changes that opinion.

Compensation

I am being compensated at $450 per hour for my expert work in this case, plus travel expenses.

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Dr. Christopher J. Portier

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Appendix: Modified tables from the Expert Report

Modified Table 1: Tumors of interest in male and female Sprague-Dawley rats the 26-month feeding study of **Lankas (1981)**[6]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	3.05	10.30	31.49	
	Female	0	3.37	11.22	34.02	
Testicular interstitial cell tumors	Male	0/50	3/50	1/50	6/50**	P_{Trend}=0.009 P_{Hist}=0.006
Interstitial cell hyperplasia	Male	1/50	1/50	1/50	0/50	P_{Trend}=0.830
Thyroid C-cell Carcinomas	Female	1/47	0/49	2/50	6/47	P_{Trend}=0.003 P_{Hist}=<0.001
Thyroid C-cell Adenomas and Carcinomas	Female	6/47	3/49	8/50	9/47	P_{Trend}=0.072 P_{Hist}=0.072
Pancreas Islet Cell Tumors	Male	0/50	5/50*	2/50	3/50	P_{Trend}=0.312
lymphocytic hyperplasia, thymus and lymph nodes	Female	27/50	35/50	38/50*	35/50	P_{Trend}=0.143
Thyroid C-cell Adenomas and Carcinomas	Male	1/47	2/49	4/49	4/49	P_{Trend}=0.122
Thyroid Follicular-cell Adenoma	Male	5/47	1/49	2/49	2/49	P_{Trend}=0.748
Liver Neoplastic Nodule	Male	3/50	5/50	1/50	3/10	P_{Trend}=0.630
Kidney Adenoma	Male	1/50	5/50	0/50	0/50	P_{Trend}=0.979
Adrenal Cortical Carcinoma	Female	5/50	10/50	6/50	4/49	P_{Trend}=0.851
Skin Keratoacanthoma	Male	0/49	0/48	0/49	0/49	P_{Trend}=1
Basal Cell Tumor	Male	0/49	0/48	0/49	1/49	P_{Trend}=0.251

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

Modified Table 2: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of **Stout and Ruecker (1990)**[9]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	89	362	940	
	Female	0	113	457	1183	
Pancreas Islet Cell Tumors (with interim sacrifice)	Male	1/58	8/57*	5/60	7/59*	P_{Trend}=0.147 P_{Hist}=0.140
Pancreas Islet Cell Tumors (without interim sacrifice)	Male	1/48	8/47*	5/50	7/49*	P_{Trend}=0.147 P_{Hist}=0.150
Hepatocellular adenomas (without interim sacrifice)	Male	3/50	2/50	3/50	8/50	P_{Trend}=0.015
Hepatocellular Adenomas and Carcinomas (without interim sacrifice)	Male	6/50	4/50	4/50	10/50	P_{Trend}=0.050
Thyroid C-Cell Adenomas (with interim sacrifice)	Female	2/60	2/60	6/60	6/60	P_{Trend}=0.050
Thyroid C-Cell Adenomas (without interim sacrifice)	Female	2/50	2/50	6/50	6/50	P_{Trend}=0.049
Thyroid C-Cell Adenomas and Carcinomas (with interim sacrifice)	Female	2/60	2/60	7/60	6/60	P_{Trend}=0.053
Thyroid C-Cell Adenomas and Carcinomas (without interim sacrifice)	Female	2/50	2/50	7/50	6/50	P_{Trend}=0.052
Thyroid C-Cell Adenomas (with interim sacrifice)	Male	2/60	4/60	8/60	7/60	P_{Trend}=0.063
Thyroid C-Cell Adenomas (without interim sacrifice)	Male	0/50	4/50	8/50**	5/50*	P_{Trend}=0.084
Thyroid C-Cell Adenomas and Carcinomas (with interim sacrifice)	Male	2/60	6/60	8/60*	8/60*	P_{Trend}=0.068
Thyroid C-Cell Adenomas and Carcinomas (without interim sacrifice)	Male	0/50	6/50*	8/50**	6/50*	P_{Trend}=0.091
Testis Interstitial Cell Tumors	Male	2/50	0/50	3/50	2/50	P_{Trend}=0.296
Kidney Adenomas	Males	0/50	2/50	0/50	0/50	P_{Trend}=0.813
Thyroid Follicular Adenoma/Carcinoma	Males	2/50	1/48	3/48	3/50	P_{Trend}=0.225
Adrenal Cortical Carcinoma	Female	0/50	0/50	0/50	3/50	P_{Trend}=0.015
Skin Keratoacanthoma	Male	1/50	3/50	4/50	5/50	P_{Trend}=0.078
Basal Cell Tumor	Male	0/50	0/50	0/50	1/50	P_{Trend}=0.250

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

Modified Table 3: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of **Atkinson et al. (1993)**[10]

Tumor	Sex	Doses (mg/kg/day)					p-values
	Male	0	11	112	320	1147	
	Female	0	12	109	347	1134	
Thyroid Follicular Adenomas and Carcinomas	Male	0/50	0/21	0/17	2/21	2/49	P_{Trend}=0.099
Thyroid Follicular Adenomas and Carcinomas (adding terminal sacrifice animals to denominator)	Male	0/50	0/50	0/50	2/50	2/49	P_{Trend}=0.034
Thyroid C-cell Adenomas and Carcinomas	Female	8/50	1/27	1/29	1/29	7/49	P_{Trend}=0.197
Thyroid C-cell Adenomas and Carcinomas	Male	9/50	1/21	1/17	2/21	9/49	P_{Trend}=0.183
Testes Interstitial Cell Tumors	Male	3/50	1/25	0/19	0/21	2/50	P_{Trend}=0.580
Kidney Adenomas	Males	1/50	0/50	0/50	0/50	0/50	p_{Trend}=1
Hepatocellular Adenomas	Males	2/50	1/50	1/50	2/50	3/50	P_{Trend}=0.155
Pancreas Islet-Cell Adenoma	Male	0/50	0/50	0/50	0/50	1/50	P_{Trend}=0.200
Skin Epithelioma (keratoacanthoma)	Male	1/50	2/25	0/19	0/21	5/50	P_{Trend}=0.047
Adrenal Cortical Carcinoma	Female	0/48	0/26	0/29	1/30	0/49	P_{Trend}=0.434
Basal Cell Tumor	Male	1/50	0/25	0/19	0/21	0/50	P_{Trend}=1

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

Modified Table 4: Tumors of interest in male and female Wistar rats from the 24-month feeding study of **Brammer (2001)**[7]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	121	361	1214	
	Female	0	145	437	1498	
Hepatocellular Adenoma	Male	0/52	2/52	0/52	5/52*	P_{Trend}=0.008
Hepatocellular Adenoma (from Greim et al., 2015[1])	Male	0/53	2/53	0/53	5/52*	P_{Trend}=0.008 P_{Hist}=0.006
Mammary Gland Adenomas and Adenocarcinomas	Female	3/51	2/51	0/51	2/51	P_{Trend}=0.575
Skin Keratocanthoma	Male	1/51	0/51	1/51	1/51	P_{Trend}=0.392
Pituitary Adenoma	Male	16/63	15/62	18/63	10/62	P_{Trend}=0.922
Pituitary Adenoma	Female	42/61	40/61	42/62	45/63	P_{Trend}=0.291

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

Modified Table 5: Tumors of interest in male and female Wistar rats from the 24-month feeding study of **Suresh(1996)**[12]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	6.3	59.4	595.2	
	Female	0	8.6	88.5	886	
Mammary Gland Adenoma and Carcinoma	Female	5/40	3/28	8/33	2/48	P_{Trend}=0.970
Hepatocellular Adenoma	Male	24/50	22/50	10/50	21/50	P_{Trend}=0.374
Skin Keratocanthoma	Male	0/50	0/50	0/50	0/50	P_{Trend}=1
Pituitary Adenoma	Male	3/49	4/30	3/31	5/49	P_{Trend}=0.376
Pituitary Adenoma	Female	7/49	13/33	7/23	6/50	P_{Trend}=0.967

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

Modified Table 6: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of **Enemoto (1997)**[11]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	104	354	1127	
	Female	0	115	393	1247	
Mammary Gland Adenoma	Female	23/50	27/50	24/50	30/50	P_{Trend}=0.106
Kidney Adenoma	Male	0/50	0/50	0/50	4/50	P_{Trend}=0.004
Thyroid C-cell Adenomas/Carcinomas	Female	4/60	7/60	8/60	4/60	P_{Trend}=0.692
Thyroid C-cell Adenomas/Carcinomas	Male	8/70	10/70	6/70	7/70	P_{Trend}=0.697
Thyroid Follicular-cell Adenomas/Carcinomas	Male	4/70	2/70	1/70	0/70	P_{Trend}=0.990
Testes Interstitial Cell Tumors	Male	3/49	2/50	0/50	2/50	P_{Trend}=0.594
Hepatocellular Adenomas	Male	1/60	0/60	2/60	1/60	P_{Trend}=0.371
Skin Keratoacanthoma[1]	Male	3/50	3/50	0/50	7/50	P_{Trend}=0.029
Pancreas Islet-Cell Adenoma	Male	4/50	1/50	2/50	1/50	P_{Trend}=0.844
Adrenal Cortical Carcinoma	Male	0/50	0/50	0/50	0/50	P_{Trend}=1
Basal Cell Tumor	Male	0/50	0/50	0/50	3/50	P_{Trend}=0.015

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1] without interim sacrifices

Modified Table 7: Tumors of interest in male and female Wistar rats from the 24-month feeding study of **Wood et al. (2009)**[8]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	85.5	285.2	1077.4	
	Female	0	104.5	348.6	1381.9	
Mammary Gland Adenomas	Female	0/51	0/51	0/51	2/51	P_{Trend}=0.062
Mammary Gland Adenocarcinomas	Female	2/51	3/51	1/51	6/51	P_{Trend}=0.042
Mammary Gland Adenomas and Adenocarcinomas	Female	2/51	3/51	1/51	8/51*	P_{Trend}=0.007
Skin Keratocanthoma	Male	2/51	3/51	0/51	6/51	P_{Trend}=0.030
Hepatocellular Adenoma	Male	0/51	2/51	1/51	1/51	P_{Trend}=0.418
Pituitary Adenoma	Male	16/51	11/51	10/51	20/51	P_{Trend}=0.045
Pituitary Adenoma	Female	24/51	13/51	16/51	32/51	P_{Trend}=0.014

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

Modified Table 9: Tumors of interest in male and female CD-1 mice from the 24-month feeding study of **Knezevich and Hogan (1983)**[2]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	157	814	4841	
	Female	0	190	955	5874	
Kidney Adenoma[1] (original pathology)	Male	0/49	0/49	1/50	3/50	P_{Trend}=0.019 P_{Hist}=0.005
Kidney Adenoma (EPA pathology)	Male	1/49	0/49	0/50	1/50	P_{Trend}=0.442 P_{Hist}=0.121
Kidney Carcinoma[2] (EPA pathology)	Male	0/49	0/49	1/50	2/50	P_{Trend}=0.063 P_{Hist}=0.002
Kidney Adenoma and Carcinoma Combined[3] (EPA pathology)	Male	1/49	0/49	1/50	3/50	P_{Trend}=0.065 P_{Hist}=0.011
Malignant Lymphoma[4]	Male	2/49	5/49	4/50	2/50	P_{Trend}=0.754 P_{Hist}=0.767
Hemangiosarcoma[5]	Male	0/50	0/49	1/50	0/50	P_{Trend}=0.503 P_{Hist}=0.591
Bilateral Chronic Interstitial Nephritis	Male	5/49	1/49	7/50	11/50	P_{Trend}=0.006
Hemangiooma[6]	Female	0/49	1/49	1/50	0/50	P_{Trend}=0.631
Lung Adenocarcinoma[7]	Male	4/48	3/50	2/50	1/50	P_{Trend}=0.918 P_{Hist}=0.899
Harderian Gland Adenoma	Female	0/49	0/49	1/50	0/50	P_{Trend}=0.505
Spleen Composite Lymphosarcoma	Female	1/49	1/49	1/50	5/50	P_{Trend}=0.015

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.27%, [2]historical rate=0.15%, [3]historical rate=0.44%, [4]historical rate=6.2%, [5]historical rate=2.5%, [6]No Historical Controls, [7]Historical rate=9.2%

Modified Table 10: Tumors of interest in male and female CD-1 mice from the 24-month feeding study of **Atkinson et al. (1993)**[17]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	98	297	988	
	Female	0	102	298	1000	
Kidney Adenoma and Carcinoma Combined[1]	Male	2/50	2/50	0/50	0/50	P_{Trend}=0.981 P_{Hist}=1
Malignant Lymphoma[2]	Male	4/50	2/50	1/50	6/50	P_{Trend}=0.087 P_{Hist}=0.085
Hemangiosarcoma[3]	Male	0/50	0/50	0/50	4/50	P_{Trend}=0.004 P_{Hist}=0.001
Hemangioma[4]	Female	0/50	0/50	0/50	0/50	P_{Trend}=1
Lung Adenocarcinoma[5]	Male	10/50	7/50	8/50	9/50	P_{Trend}=0.456 P_{Hist}=0.449
Harderian Gland Adenoma	Female	Not examined				

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.44%, [2]historical rate=6.2%, [3]historical rate=2.5%, [4]No historical control rate, [5]Historical rate=9.2%

Modified Table 11: Tumors of interest in male and female CD-1 mice from the 18-month feeding study of **Wood et al. (2009)**[13]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	71.4	234.2	810	
	Female	0	97.9	299.5	1081.2	
Kidney Adenoma[1]	Male	0/51	0/51	0/51	0/51	$P_{Trend}=1$
Malignant Lymphoma[2]	Male	0/51	1/51	2/51	5/51*	$P_{Trend}=0.007$ $P_{Hist}=0.007$
Hemangiosarcoma	Male	0/51	0/51	0/51	0/51	$P_{Trend}=1$
Lung Adenocarcinoma[3]	Male	5/51	5/51	7/51	11/51	$p_{Trend}=0.028$ $P_{Hist}=0.031$
Hemangioma[4]	Female	0/51	2/51	0/51	1/51	$p_{Trend}=0.438$
Harderian Gland	Female	1/51	0/51	0/51	2/51	$p_{Trend}=0.155$
Animals with Malignant Neoplasms	Male	14/51	20/51	17/51	20/51	$P_{Trend}=0.203$
Animals with Malignant Neoplasms	Female	23/51	15/51	17/51	18/51	$P_{Trend}=0.628$
Animals with multiple malignant tumors	Male	1/51	2/51	3/51	5/51	$P_{Trend}=0.046$

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$, [1]historical rate=0.44%, [2]historical rate=2.6%, [3]Historical rate=2.5%, [4]No Historical Control Rate

Modified Table 12: Tumors of interest in male and female CD-1 mice from the 18-month feeding study of **Sugimoto (1997)**[3]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	165	838.1	4348	
	Female	0	153.2	786.8	4116	
Kidney Adenoma[1]	Male	0/50	0/50	0/50	2/50	P_{Trend}=0.062 P_{Hist}=0.005
Malignant Lymphoma[2]	Male	2/50	2/50	0/50	6/50	P_{Trend}=0.016 P_{Hist}=0.017
Hemangiosarcoma[3]	Male	0/50	0/50	0/50	2/50	P_{Trend}=0.062 P_{Hist}=0.004
Hemangioma[4]	Female	0/50	0/50	2/50	5/50*	P_{Trend}=0.002
Lung Adenocarcinoma[5]	Male	1/50	1/50	6/50	4/50	P_{Trend}=0.148 P_{Hist}=0.140
Harderian Gland Adenoma	Female	1/50	3/50	0/50	5/50	P_{Trend}=0.040
Number of animals with Malignant Neoplasms	Male	5/50	5/50	11/50	16/50**	P_{Trend}=0.001
Number of animals with Malignant Neoplasms	Female	9/50	13/50	16/50	13/50	P_{Trend}=0.362

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.44%, [2]historical rate=2.6%, [3]historical rate=0/1424 (0.26% - 95% confidence limit), [4]No Historical Control Rate, [5]Historical rate=2.5%

Modified Table 15: Observed versus expected tumor sites with significant trends in the 12 acceptable rodent carcinogenicity studies using glyphosate.

Species	Strain	Sex	Total Sites[1]	Exp. <0.05	Obs. <0.05	Tumors[2] p<0.05	Exp. <0.01	Obs. <0.01	Tumors p<0.01
Rat (7 studies)	Sprague-Dawley (4 studies)	M	86	4.3	9	TICT, TFAC, KA, HA, HAC, SE, SK(2)[3], BC	0.9	2	TICT, KA
		F	80	4	3	TCCA, TCCC, AC	0.8	1	TCCC
	Wistar (3 studies)	M	64.5	3.2	3	HA, SK, PA	0.6	1	HA
		F	60	3	3	MC, MAC, PA	0.6	1	MAC
Mouse (5 studies)	CD-1 (4 studies)	M	42	2.1	8	KA, KC, KAC, HS(2), ML(2), LAC	0.4	5	KA,KC, HS(2), ML
		F	60	3	3	H, SL, HGA	0.6	1	H
	Albino (1 study)	M	10.5	0.5	0		0.1	0	
		F	15	0.8	1	H	0.2	1	H
Rats (7 studies)	All (7 studies)	M	150.5	7.5	11	TICT, TFAC, KA, HA(2), HAC, SE, SK(3), BC, PA	1.5	3	TICT, KA, HA
		F	140	7	6	TCCA, TCCC, AC, MC, MAC, PA	1.4	2	TCCC, MAC
		Both	295.5	14.5	19	TICT, TFAC, KA, HA(2), HAC, SE, SK(3), BC, PA(2), TCCA, TCCC, AC, MC, MAC	3.0	5	TICT, KA, HA, TCCC, MAC
Mice (5 studies)	All (5 studies)	M	52.5	2.6	8	KA, KC, KAC, HS(2), ML(2), LAC	0.5	5	KA,KC, HS(2), ML
		F	75	3.8	4	H(2), SL, HGA	0.7	2	H(2)
		Both	127.5	6.4	12	KA, KC, KAC, HS(2), H(2), ML(2), LAC,SL, HGA	1.3	7	KA,KC, HS(2), H(2), ML
All (12 studies)	All (12 studies)	M	203	10.1	20	TICT, TFAC, KA(2), HA(2), HAC, SE, SK(3), BC, PA, KC, KAC, HS(2), ML(2), LAC	2.0	8	TICT, HA, KA(2),KC, HS(2), ML
		F	215	10.8	10	TCCA, TCCC, MC, MAC, H(2), AC, PA, SL, HGA	2.2	4	TCCC, MAC, H(2)
		Both	418	20.9	30	TICT, TFAC, KA(2), HA(2), HAC, SE, SK(3), BC, PA(2), KC, KAC, HS(2), ML(2), LAC, TCCA, TCCC, MC, MAC, H(2), AC, SL, HGA	4.2	12	TICT, HA, KA(2), KC, HS(2), H(2), ML, TCCC, MAC

[1]Number of sites examined is based upon suggestions by Dr. J. Haseman in his written testimony to the EPA with female rats modified for fewer sites with 3 or more tumors; male mice – 10.5 sites; female mice – 15 sites; male rats – 21.5 sites; female rats – 20 sites

[2]Tumor abbreviations are: KA – kidney adenoma; KC – kidney carcinoma; KAC – kidney adenoma or carcinoma; HS – hemangiosarcoma; H – hemangioma; HA – hepatocellular adenoma; LAC – lung adenoma or adenocarcinoma; ML – malignant lymphoma; MC – mammary gland carcinoma; MAC – mammary gland adenoma or carcinoma; TCCA – thyroid C-cell adenoma; TCCC – thyroid C-cell carcinoma; TFAC – thyroid follicular cell adenoma or carcinoma; TICT – testes interstitial cell tumor; SK – skin keratoacanthoma; SE – skin epithelioma; AC – adrenal cortical carcinoma; BC – basal cell tumor; PA – pituitary adenoma; SL – skin lymphoma; HGA – Harderian gland adenoma

[3](x): x studies with this result