UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: December 12, 2017

SUBJECT: Updated Statistics Performed on Animal Carcinogenicity Study Data for Glyphosate

PC Code: 417300; 103601; 103603; 103604; 103605; 103607; 103608; 103613
Decision Number: 487242
Petition Number: NA
Risk Assessment Type: NA
TXR Number: 0057690

MRID Numbers: NA

DP Barcode: D444708

Registration Numbers: NA
Regulatory Action: Registration Review
Case Number: 178
CAS Number: 1071-83-6; 38641-94-0; 70393-85-0; 114370-14-8; 40465-76-7; 69254-40-6; 34494-04-7; 70901-12-1
40 CFR: 180.364

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TO: Christine L. Olinger, Branch Chief
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In December 2016, a Scientific Advisory Panel (SAP) meeting was held to evaluate the human carcinogenic potential of glyphosate. As part of this evaluation, statistical analyses of tumor incidences observed in rat and mouse carcinogenicity studies were performed (D435608). These analyses included the Cochran-Armitage Test for Trend, the Fisher Exact Test, and use of the Sidak Correction Method to adjust for multiple comparisons. In the SAP final report[1], the SAP panel noted that the Sidak correction would not be appropriate since it assumes independence and suggested the Benjamini-Hochberg correction should be applied instead. Furthermore, the SAP recommended the multiple comparison correction should be applied to the trend test since

[1] https://www.epa.gov/sites/production/files/2017-03/documents/december_13-16_2016_final_report_03162017.pdf

the trend test and pairwise comparisons are being used together. As a result, the statistical analyses have been updated to reflect these recommendations. Additionally, as part of this update, it was noted that some of the statistical analyses included animals sacrificed at an interim time point and animals that died prior to the interim sacrifice (Lankas, 1981; Wood et al., 2009a; Brammer, 2001; Sugimoto, 1997; Wood et al., 2009b). To be consistent across all of the studies, these animals have now been excluded from the statistical analyses. Below are the results of the updated analyses.

Lankas, 1981 (MRID 00093879) - rat

Testicular interstitial tumors - males

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**3.05**	**10.3**	**31.49**	**Total**
N	47 100.00	46 93.88	46 97.87	44 88.00	183
Y	0 0.00	3 6.12	1 2.13	6 12.00	10
Total	47	49	47	50	193

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
testicular_tumor	(0, 3.05, 10.3, 31.49)	Cochran-Armitage Trend, 1-sided	0.011	0.032
testicular_tumor	(0, 3.05)	FISHER'S EXACT, right-sided	0.129	0.172
testicular_tumor	(0, 10.3)	FISHER'S EXACT, right-sided	0.500	0.500
testicular_tumor	(0, 31.49)	FISHER'S EXACT, right-sided	0.016	0.032

Wood et al., 2009 (MRID 49957404) - rat

Mammary gland adenomas - females

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**95**	**316.9**	**1229.7**	**Total**
N	48 100.00	51 100.00	50 100.00	48 96.00	197
Y	0 0.00	0 0.00	0 0.00	2 4.00	2
Total	48	51	50	50	199

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
adenomas	(0, 95, 316.9, 1229.7)	Cochran-Armitage Trend, 1-sided	0.062	0.124
adenomas	(0, 1229.7)	FISHER'S EXACT, right-sided	0.258	0.258

Mammary gland adenocarcinomas - females

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	95	316.9	1229.7	Total
N	46 95.83	48 94.12	49 98.00	44 88.00	187
Y	2 4.17	3 5.88	1 2.00	6 12.00	12
Total	48	51	50	50	199

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
adenocarcinomas	(0, 95, 316.9, 1229.7)	Cochran-Armitage Trend, 1-sided	0.043	0.172
adenocarcinomas	(0, 95)	FISHER'S EXACT, right-sided	0.529	0.705
adenocarcinomas	(0, 316.9)	FISHER'S EXACT, right-sided	0.886	0.886
adenocarcinomas	(0, 1229.7)	FISHER'S EXACT, right-sided	0.148	0.296

Mammary gland combined adenomas/adenocarcinomas – females

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	95	316.9	1229.7	Total
N	46 95.83	48 94.12	49 98.00	42 84.00	185
Y	2 4.17	3 5.88	1 2.00	8 16.00	14
Total	48	51	50	50	199

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
adenomas_adenocarcinomas	(0, 95, 316.9, 1229.7)	Cochran-Armitage Trend, 1-sided	0.007	0.028
adenomas_adenocarcinomas	(0, 95)	FISHER'S EXACT, right-sided	0.529	0.705
adenomas_adenocarcinomas	(0, 316.9)	FISHER'S EXACT, right-sided	0.886	0.886
adenomas_adenocarcinomas	(0, 1229.7)	FISHER'S EXACT, right-sided	0.053	0.105

Stout and Ruecker, 1990 (MRID 41643801) - rat

Thyroid C-Cell Adenomas – males

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	89	362	940	Total
N	52 96.30	51 92.73	50 86.21	51 87.93	204
Y	2 3.70	4 7.27	8 13.79	7 12.07	21
Total	54	55	58	58	225

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Adenomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.079	0.132
Adenomas	(0, 89)	FISHER'S EXACT, right-sided	0.348	0.348
Adenomas	(0, 362)	FISHER'S EXACT, right-sided	0.060	0.132
Adenomas	(0, 940)	FISHER'S EXACT, right-sided	0.099	0.132

Thyroid C-cell Carcinoma – males

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	89	362	940	Total
N	54 100.00	53 96.36	58 100.00	57 98.28	222
Y	0 0.00	2 3.64	0 0.00	1 1.72	3
Total	54	55	58	58	225

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Carcinomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.457	0.518
Carcinomas	(0, 89)	FISHER'S EXACT, right-sided	0.252	0.518
Carcinomas	(0, 940)	FISHER'S EXACT, right-sided	0.518	0.518

Thyroid C-Cell Combined Adenomas/Carcinomas – males

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**89**	**362**	**940**	**Total**
N	52 96.30	49 89.09	50 86.21	50 86.21	201
Y	2 3.70	6 10.91	8 13.79	8 13.79	24
Total	54	55	58	58	225

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Adenomas_Carcinomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.087	0.116
Adenomas_Carcinomas	(0, 89)	FISHER'S EXACT, right-sided	0.141	0.141
Adenomas_Carcinomas	(0, 362)	FISHER'S EXACT, right-sided	0.060	0.116
Adenomas_Carcinomas	(0, 940)	FISHER'S EXACT, right-sided	0.060	0.116

Thyroid C-Cell Adenomas – females

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**113**	**457**	**1183**	**Total**
N	55 96.49	58 96.67	53 89.83	49 89.09	215
Y	2 3.51	2 3.33	6 10.17	6 10.91	16
Total	57	60	59	55	231

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Adenomas	(0, 113, 457, 1183)	Cochran-Armitage Trend, 1-sided	0.040	0.159
Adenomas	(0, 113)	FISHER'S EXACT, right-sided	0.710	0.710
Adenomas	(0, 457)	FISHER'S EXACT, right-sided	0.147	0.196
Adenomas	(0, 1183)	FISHER'S EXACT, right-sided	0.124	0.196

Thyroid C-Cell Carcinomas – females

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**113**	**457**	**1183**	**Total**
N	57 100.00	60 100.00	58 98.31	55 100.00	230
Y	0 0.00	0 0.00	1 1.69	0 0.00	1
Total	57	60	59	55	231

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Carcinomas	(0, 113, 457, 1183)	Cochran-Armitage Trend, 1-sided	0.494	0.509
Carcinomas	(0, 457)	FISHER'S EXACT, right-sided	0.509	0.509

Thyroid C-Cell Combined Adenomas/Carcinomas – females

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	113	457	1183	Total
N	55 96.49	58 96.67	52 88.14	49 89.09	214
Y	2 3.51	2 3.33	7 11.86	6 10.91	17
Total	57	60	59	55	231

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Adenomas_Carcinomas	(0, 113, 457, 1183)	Cochran-Armitage Trend, 1-sided	0.042	0.166
Adenomas_Carcinomas	(0, 113)	FISHER'S EXACT, right-sided	0.710	0.710
Adenomas_Carcinomas	(0, 457)	FISHER'S EXACT, right-sided	0.090	0.166
Adenomas_Carcinomas	(0, 1183)	FISHER'S EXACT, right-sided	0.124	0.166

Pancreatic Adenomas – males

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	89	362	940	Total
N	42 97.67	37 82.22	44 89.80	41 85.42	164
Y	1 2.33	8 17.78	5 10.20	7 14.58	21
Total	43	45	49	48	185

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Adenomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.176	0.176
Adenomas	(0, 89)	FISHER'S EXACT, right-sided	0.018	0.071
Adenomas	(0, 362)	FISHER'S EXACT, right-sided	0.135	0.176
Adenomas	(0, 940)	FISHER'S EXACT, right-sided	0.042	0.083

Pancreatic Carcinomas – males

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**89**	**362**	**940**	**Total**
N	42 97.67	45 100.00	49 100.00	48 100.00	184
Y	1 2.33	0 0.00	0 0.00	0 0.00	1
Total	43	45	49	48	185

No trend test or pairwise comparisons are shown since tumor incidence decreased with increasing dose.

Pancreatic Combined Adenomas and Carcinomas – males

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**89**	**362**	**940**	**Total**
N	41 95.35	37 82.22	44 89.80	41 85.42	163
Y	2 4.65	8 17.78	5 10.20	7 14.58	22
Total	43	45	49	48	185

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Adenomas_Carcinomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.242	0.275
Adenomas_Carcinomas	(0, 89)	FISHER'S EXACT, right-sided	0.052	0.209
Adenomas_Carcinomas	(0, 362)	FISHER'S EXACT, right-sided	0.275	0.275
Adenomas_Carcinomas	(0, 940)	FISHER'S EXACT, right-sided	0.108	0.215

Hepatocellular Adenomas – males

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**89**	**362**	**940**	**Total**
N	42 95.45	43 95.56	46 93.88	41 85.42	172
Y	2 4.55	2 4.44	3 6.12	7 14.58	14
Total	44	45	49	48	186

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Adenomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.022	0.089
Adenomas	(0, 89)	FISHER'S EXACT, right-sided	0.700	0.700
Adenomas	(0, 362)	FISHER'S EXACT, right-sided	0.551	0.700
Adenomas	(0, 940)	FISHER'S EXACT, right-sided	0.101	0.202

Hepatocellular Carcinomas – males

Table of incident by Doses					
incident	**Doses**				
Frequency **Col Pct**	**0**	**89**	**362**	**940**	**Total**
N	41 93.18	43 95.56	48 97.96	46 95.83	178
Y	3 6.82	2 4.44	1 2.04	2 4.17	8
Total	44	45	49	48	186

No trend test or pairwise comparisons are shown since tumor incidence decreased with increasing dose.

Hepatocellular Combined Adenomas and Carcinomas – males

Table of incident by Doses					
incident	**Doses**				
Frequency **Col Pct**	**0**	**89**	**362**	**940**	**Total**
N	39 88.64	41 91.11	45 91.84	39 81.25	164
Y	5 11.36	4 8.89	4 8.16	9 18.75	22
Total	44	45	49	48	186

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Adenomas_Carcinomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.078	0.312
Adenomas_Carcinomas	(0, 89)	FISHER'S EXACT, right-sided	0.769	0.808
Adenomas_Carcinomas	(0, 362)	FISHER'S EXACT, right-sided	0.808	0.808
Adenomas_Carcinomas	(0, 940)	FISHER'S EXACT, right-sided	0.245	0.489

Brammer, 2001 (MRID 49704601)

Hepatocellular Adenomas – males

Table of incident by Doses					
incident	**Doses**				
Frequency **Col Pct**	**0**	**121**	**361**	**1214**	**Total**
N	44 100.00	46 95.83	48 100.00	44 89.80	182
Y	0 0.00	2 4.17	0 0.00	5 10.20	7
Total	44	48	48	49	189

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Adenomas	(0, 121, 361, 1214)	Cochran-Armitage Trend, 1-sided	0.010	0.029
Adenomas	(0, 121)	FISHER'S EXACT, right-sided	0.269	0.269
Adenomas	(0, 1214)	FISHER'S EXACT, right-sided	0.037	0.055

Knezevich and Hogan, 1983 (MRID 00130406) - mouse

Kidney Adenomas - males

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	161	835	4945	Total
N	48 97.96	49 100.00	50 100.00	49 98.00	196
Y	1 2.04	0 0.00	0 0.00	1 2.00	2
Total	49	49	50	50	198

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Adenomas	(0, 161, 835, 4945)	Cochran-Armitage Trend, 1-sided	0.442	1.000
Adenomas	(0, 161)	FISHER'S EXACT, right-sided	1.000	1.000
Adenomas	(0, 835)	FISHER'S EXACT, right-sided	1.000	1.000
Adenomas	(0, 4945)	FISHER'S EXACT, right-sided	0.758	1.000

Kidney Carcinomas – males

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	161	835	4945	Total
N	49 100.00	49 100.00	49 98.00	48 96.00	195
Y	0 0.00	0 0.00	1 2.00	2 4.00	3
Total	49	49	50	50	198

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Carcinomas	(0, 161, 835, 4945)	Cochran-Armitage Trend, 1-sided	0.063	0.190
Carcinomas	(0, 835)	FISHER'S EXACT, right-sided	0.505	0.505
Carcinomas	(0, 4945)	FISHER'S EXACT, right-sided	0.253	0.379

Kidney Combined Adenomas/Carcinomas – males

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	161	835	4945	Total
N	48 97.96	49 100.00	49 98.00	47 94.00	193
Y	1 2.04	0 0.00	1 2.00	3 6.00	5
Total	49	49	50	50	198

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
combined	(0, 161, 835, 4945)	Cochran-Armitage Trend, 1-sided	0.065	0.259
combined	(0, 161)	FISHER'S EXACT, right-sided	1.000	1.000
combined	(0, 835)	FISHER'S EXACT, right-sided	0.758	1.000
combined	(0, 4945)	FISHER'S EXACT, right-sided	0.316	0.633

Sugimoto, 1997 (MRID 50017108-50017109) - mouse

Hemangiomas – females

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	153.2	786.8	4116	Total
N	48 100.00	47 100.00	43 95.56	40 88.89	178
Y	0 0.00	0 0.00	2 4.44	5 11.11	7
Total	48	47	45	45	185

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Hemangiomas	(0, 153.2, 786.8, 4116)	Cochran-Armitage Trend, 1-sided	0.002	0.005
Hemangiomas	(0, 786.8)	FISHER'S EXACT, right-sided	0.231	0.231
Hemangiomas	(0, 4116)	FISHER'S EXACT, right-sided	0.024	0.035

Wood et al., 2009 (MRID 49957402) – mouse

Malignant lymphoma – males

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**71.4**	**234.2**	**810**	**Total**
N	44 100.00	45 97.83	46 95.83	40 88.89	175
Y	0 0.00	1 2.17	2 4.17	5 11.11	8
Total	44	46	48	45	183

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
lymphoma	(0, 71.4, 234.2, 810)	Cochran-Armitage Trend, 1-sided	0.006	0.025
lymphoma	(0, 71.4)	FISHER'S EXACT, right-sided	0.511	0.511
lymphoma	(0, 234.2)	FISHER'S EXACT, right-sided	0.269	0.359
lymphoma	(0, 810)	FISHER'S EXACT, right-sided	0.029	0.059

Lung Adenomas – males

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**71.4**	**234.2**	**810**	**Total**
N	35 79.55	39 84.78	39 81.25	41 91.11	154
Y	9 20.45	7 15.22	9 18.75	4 8.89	29
Total	44	46	48	45	183

No trend test or pairwise comparisons are shown since tumor incidence decreased with increasing dose.

Lung Adenocarcinomas – males

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**71.4**	**234.2**	**810**	**Total**
N	39 88.64	41 89.13	41 85.42	34 75.56	155
Y	5 11.36	5 10.87	7 14.58	11 24.44	28
Total	44	46	48	45	183

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
adenocarcinomas	(0, 71.4, 234.2, 810)	Cochran-Armitage Trend, 1-sided	0.026	0.103
adenocarcinomas	(0, 71.4)	FISHER'S EXACT, right-sided	0.659	0.659
adenocarcinomas	(0, 234.2)	FISHER'S EXACT, right-sided	0.443	0.590
adenocarcinomas	(0, 810)	FISHER'S EXACT, right-sided	0.091	0.182

Lung Combined Adenomas/Adenocarcinomas – males

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**71.4**	**234.2**	**810**	**Total**
N	30 68.18	34 73.91	32 66.67	30 66.67	126
Y	14 31.82	12 26.09	16 33.33	15 33.33	57
Total	44	46	48	45	183

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
Incidence	(0, 71.4, 234.2, 810)	Cochran-Armitage Trend, 1-sided	0.328	0.706
Incidence	(0, 71.4)	FISHER'S EXACT, right-sided	0.797	0.797
Incidence	(0, 234.2)	FISHER'S EXACT, right-sided	0.527	0.706
Incidence	(0, 810)	FISHER'S EXACT, right-sided	0.529	0.706

Atkinson 1993 (MRID 49631702) - mouse

Hemangiosarcomas - males

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**100**	**300**	**1000**	**Total**
N	47 100.00	46 100.00	50 100.00	41 91.11	184
Y	0 0.00	0 0.00	0 0.00	4 8.89	4
Total	47	46	50	45	188

Variable	comparison	Test	Raw p-value	False Discovery Rate p-value
hemangiosarcoma	(0, 100, 300, 1000)	Cochran-Armitage Trend, 1-sided	0.003	0.006
hemangiosarcoma	(0, 1000)	FISHER'S EXACT, right-sided	0.053	0.053