UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: September 9, 2016

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

PC Code: 417300; 103601; 103603; 103604; 103605; 103607; 103608; 103613;
Decision Number: 521043
Petition Number: NA
Risk Assessment Type: NA
TXR Number: 0057494

MRID Numbers: NA

DP Barcode: D435608

Registration Numbers: NA
Regulatory Action: Registration Review
Case Number: 178
CAS Number: 1071-83-63; 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: Kelly M. Lowe, Acting Branch Chief
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As part of the 2016 registration review of glyphosate, statistics were performed on all relevant tumor data identified in animal carcinogenicity studies. According to the 2005 Guidelines for Carcinogen Risk Assessment, trend tests and pairwise comparison tests are the recommended tests for statistical analyses of tumor data. The Cochran-Armitage Test for Trend (Snedecor and Cochran, 1967; one-sided) was used to evaluate whether individual tumor data demonstrated a linear trend. The Fisher Exact Test (Fisher, 1950; one-sided) was used for pairwise comparisons to determine if incidences observed in treated groups were statistically different from concurrent controls. A Sidak correction method was used to adjust for multiple comparisons. As a result, raw unadjusted and Sidak adjusted values are presented. Below are the results of the updated analyses.

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Lankas, 1981 (MRID 00093879) - rat

Testicular interstitial tumors - males

Table of Interstitial by Group					
Interstitial	Group				
Frequency Col Pct	0	3.05	10.3	31.49	Total
N	50 100.00	47 94.00	49 98.00	44 88.00	190
Y	0 0.00	3 6.00	1 2.00	6 12.00	10
Total	50	50	50	50	200

Cochran-Armitage trend test and Fisher's Exact Test			
comparison	Test	Raw p-value	Sidak p-value
(0,3.05,10.3,31.49)	Cochran-Armitage Trend, 1-side	0.009	.
(0,3.05)	FISHER'S EXACT, 1-side	0.121	0.321
(0,10.3)	FISHER'S EXACT, 1-side	0.500	0.875
(0,31.49)	FISHER'S EXACT, 1-side	0.013	0.039

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

Mammary gland adenomas - females

Table of adenomas by Group					
adenomas	Group				
Frequency Col Pct	0	95	316.9	1229.7	Total
N	51 100.00	51 100.00	51 100.00	49 96.08	202
Y	0 0.00	0 0.00	0 0.00	2 3.92	2
Total	51	51	51	51	204

Cochran-Armitage trend test and Fisher's Exact Test			
comparison	Test	Raw p-value	Sidak p-value
(0,95,316.9,1229.7)	Cochran-Armitage Trend, 1-side	0.062	.
(0,1229.7)	FISHER'S EXACT, 1-side	0.248	0.248

Mammary gland adenocarcinomas - females

Table of adenocarcinomas by Group					
adenocarcinomas	Group				
Frequency Col Pct	0	95	316.9	1229.7	Total
N	49 96.08	48 94.12	50 98.04	45 88.24	192
Y	2 3.92	3 5.88	1 1.96	6 11.76	12
Total	51	51	51	51	204

Cochran-Armitage trend test and Fisher's Exact Test			
comparison	**Test**	**Raw p-value**	**Sidak p-value**
(0,95,316.9,1229.7)	Cochran-Armitage Trend, 1-side	0.042	.
(0,95)	FISHER'S EXACT, 1-side	0.500	0.875
(0,316.9)	FISHER'S EXACT, 1-side	0.879	0.998
(0,1229.7)	FISHER'S EXACT, 1-side	0.135	0.352

Mammary gland combined adenomas/adenocarcinomas – females

Table of combined adenomas/adenocarcinomas by Group					
Adenomas or adenocarcinomas	**Group**				
Frequency Col Pct	**0**	**95**	**316.9**	**1229.7**	**Total**
N	49 96.08	48 94.12	50 98.04	43 84.31	190
Y	2 3.92	3 5.88	1 1.96	8 15.69	14
Total	51	51	51	51	204

Cochran-Armitage trend test and Fisher's Exact Test			
comparison	**Test**	**Raw p-value**	**Sidak p-value**
(0,95,316.9,1229.7)	Cochran-Armitage Trend, 1-side	0.007	.
(0,95)	FISHER'S EXACT, 1-side	0.500	0.875
(0,316.9)	FISHER'S EXACT, 1-side	0.879	0.998
(0,1229.7)	FISHER'S EXACT, 1-side	0.046	0.132

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	Sidak p-value
Adenomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.079	.
Adenomas	(0, 89)	FISHER'S EXACT, right-sided	0.348	0.723
Adenomas	(0, 362)	FISHER'S EXACT, right-sided	0.060	0.168
Adenomas	(0, 940)	FISHER'S EXACT, right-sided	0.099	0.269

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	Sidak p-value
Carcinomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.457	.
Carcinomas	(0, 89)	FISHER'S EXACT, right-sided	0.252	0.441
Carcinomas	(0, 940)	FISHER'S EXACT, right-sided	0.518	0.768

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	Sidak p-value
Adenomas_Carcinomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.087	.
Adenomas_Carcinomas	(0, 89)	FISHER'S EXACT, right-sided	0.141	0.367
Adenomas_Carcinomas	(0, 362)	FISHER'S EXACT, right-sided	0.060	0.168
Adenomas_Carcinomas	(0, 940)	FISHER'S EXACT, right-sided	0.060	0.168

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	Sidak p-value
Adenomas	(0, 113, 457, 1183)	Cochran-Armitage Trend, 1-sided	0.040	.
Adenomas	(0, 113)	FISHER'S EXACT, right-sided	0.710	0.976
Adenomas	(0, 457)	FISHER'S EXACT, right-sided	0.147	0.380
Adenomas	(0, 1183)	FISHER'S EXACT, right-sided	0.124	0.328

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	Sidak p-value
Carcinomas	(0, 113, 457, 1183)	Cochran-Armitage Trend, 1-sided	0.494	.
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	Sidak p-value
Adenomas_Carcinomas	(0, 113, 457, 1183)	Cochran-Armitage Trend, 1-sided	0.042	.
Adenomas_Carcinomas	(0, 113)	FISHER'S EXACT, right-sided	0.710	0.976
Adenomas_Carcinomas	(0, 457)	FISHER'S EXACT, right-sided	0.090	0.246
Adenomas_Carcinomas	(0, 1183)	FISHER'S EXACT, right-sided	0.124	0.328

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

Table of incident by Doses					
incident	**Doses**				
Frequency Col Pct	**0**	**89**	**362**	**940**	**Total**
Total	43	45	49	48	185

Variable	comparison	Test	Raw p-value	Sidak p-value
Adenomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.176	.
Adenomas	(0, 89)	FISHER'S EXACT, right-sided	0.018	0.052
Adenomas	(0, 362)	FISHER'S EXACT, right-sided	0.135	0.352
Adenomas	(0, 940)	FISHER'S EXACT, right-sided	0.042	0.120

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

Variable	comparison	Test	Raw p-value	Sidak p-value
Carcinomas	(0, 89)	FISHER'S EXACT, right-sided	1.000	1.000
Carcinomas	(0, 362)	FISHER'S EXACT, right-sided	1.000	1.000
Carcinomas	(0, 940)	FISHER'S EXACT, right-sided	1.000	1.000

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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	Sidak p-value
Adenomas_Carcinomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.242	.
Adenomas_Carcinomas	(0, 89)	FISHER'S EXACT, right-sided	0.052	0.149
Adenomas_Carcinomas	(0, 362)	FISHER'S EXACT, right-sided	0.275	0.619
Adenomas_Carcinomas	(0, 940)	FISHER'S EXACT, right-sided	0.108	0.289

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	Sidak p-value
Adenomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.022	.
Adenomas	(0, 89)	FISHER'S EXACT, right-sided	0.700	0.973
Adenomas	(0, 362)	FISHER'S EXACT, right-sided	0.551	0.910
Adenomas	(0, 940)	FISHER'S EXACT, right-sided	0.101	0.274

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

Variable	comparison	Test	Raw p-value	Sidak p-value
Carcinomas	(0, 89)	FISHER'S EXACT, right-sided	0.827	0.995
Carcinomas	(0, 362)	FISHER'S EXACT, right-sided	0.954	1.000
Carcinomas	(0, 940)	FISHER'S EXACT, right-sided	0.845	0.996

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

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	89	362	940	Total
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	Sidak p-value
Adenomas_Carcinomas	(0, 89, 362, 940)	Cochran-Armitage Trend, 1-sided	0.078	.
Adenomas_Carcinomas	(0, 89)	FISHER'S EXACT, right-sided	0.769	0.988
Adenomas_Carcinomas	(0, 362)	FISHER'S EXACT, right-sided	0.808	0.993
Adenomas_Carcinomas	(0, 940)	FISHER'S EXACT, right-sided	0.245	0.569

Brammer, 2001 (MRID 49704601)

Hepatocellular Adenomas - males

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	121	361	1214	Total
N	52 100.00	50 96.15	52 100.00	47 90.38	201
Y	0 0.00	2 3.85	0 0.00	5 9.62	7
Total	52	52	52	52	208

Variable	comparison	Test	Raw p-value	Sidak p-value
Adenomas	(0, 121, 361, 1214)	Cochran-Armitage Trend, 1-sided	0.008	.
Adenomas	(0, 121)	FISHER'S EXACT, right-sided	0.248	0.434
Adenomas	(0, 1214)	FISHER'S EXACT, right-sided	0.028	0.056

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	Sidak p-value
Adenomas	(0, 161, 835, 4945)	Cochran-Armitage Trend, 1-sided	0.442	.
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	0.986

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	Sidak p-value
Carcinomas	(0, 161, 835, 4945)	Cochran-Armitage Trend, 1-sided	0.063	.
Carcinomas	(0, 835)	FISHER'S EXACT, right-sided	0.505	0.755
Carcinomas	(0, 4945)	FISHER'S EXACT, right-sided	0.253	0.441

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	Sidak p-value
combined	(0, 161, 835, 4945)	Cochran-Armitage Trend, 1-sided	0.065	.
combined	(0, 161)	FISHER'S EXACT, right-sided	1.000	1.000
combined	(0, 835)	FISHER'S EXACT, right-sided	0.758	0.986
combined	(0, 4945)	FISHER'S EXACT, right-sided	0.316	0.680

<u>Sugimoto, 1997 (MRID 50017108-50017109) - mouse</u>

Hemangiomas – females

Table of Hemangiomas by Group					
Hemangiomas	Group				
Frequency Col Pct	0	165	838.1	4348	Total
N	50 100.00	50 100.00	48 96.00	45 90.00	193
Y	0 0.00	0 0.00	2 4.00	5 10.00	7
Total	50	50	50	50	200

Cochran-Armitage trend test and Fisher's Exact Test			
comparison	**Test**	**Raw p-value**	**Sidak p-value**
(0,165,838.1,4348)	Cochran-Armitage Trend, 1-side	0.002	.
(0,838.1)	FISHER'S EXACT, 1-side	0.247	0.434
(0,4348)	FISHER'S EXACT, 1-side	0.028	0.055

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	51 100.00	50 98.04	49 96.08	46 90.20	196
Y	0 0.00	1 1.96	2 3.92	5 9.80	8
Total	51	51	51	51	204

Variable	comparison	Test	Raw p-value	Sidak p-value
lymphoma	(0, 71.4, 234.2, 810)	Cochran-Armitage Trend, 1-sided	0.007	.
lymphoma	(0, 71.4)	FISHER'S EXACT, right-sided	0.500	0.875
lymphoma	(0, 234.2)	FISHER'S EXACT, right-sided	0.248	0.574
lymphoma	(0, 810)	FISHER'S EXACT, right-sided	0.028	0.082

Lung Adenomas - males

Table of incident by Doses					
incident	**Doses**				
Frequency **Col Pct**	**0**	**71.4**	**234.2**	**810**	**Total**
N	42 82.35	44 86.27	42 82.35	47 92.16	175
Y	9 17.65	7 13.73	9 17.65	4 7.84	29
Total	51	51	51	51	204

Variable	comparison	Test	Raw p-value	Sidak p-value
adenomas	(0, 71.4)	FISHER'S EXACT, right-sided	0.793	0.991
adenomas	(0, 234.2)	FISHER'S EXACT, right-sided	0.602	0.937
adenomas	(0, 810)	FISHER'S EXACT, right-sided	0.964	1.000

Lung Adenocarcinomas – males

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	71.4	234.2	810	Total
N	46 90.20	46 90.20	44 86.27	40 78.43	176
Y	5 9.80	5 9.80	7 13.73	11 21.57	28
Total	51	51	51	51	204

Variable	comparison	Test	Raw p-value	Sidak p-value
adenocarcinomas	(0, 71.4, 234.2, 810)	Cochran-Armitage Trend, 1-sided	0.028	.
adenocarcinomas	(0, 71.4)	FISHER'S EXACT, right-sided	0.630	0.949
adenocarcinomas	(0, 234.2)	FISHER'S EXACT, right-sided	0.380	0.762
adenocarcinomas	(0, 810)	FISHER'S EXACT, right-sided	0.086	0.237

Lung Combined Adenomas/Adenocarcinomas – males

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	71.4	234.2	810	Total
N	37 72.55	39 76.47	35 68.63	36 70.59	147
Y	14 27.45	12 23.53	16 31.37	15 29.41	57
Total	51	51	51	51	204

Variable	comparison	Test	Raw p-value	Sidak p-value
Incidence	(0, 71.4, 234.2, 810)	Cochran-Armitage Trend, 1-sided	0.336	.
Incidence	(0, 71.4)	FISHER'S EXACT, right-sided	0.752	0.985
Incidence	(0, 234.2)	FISHER'S EXACT, right-sided	0.414	0.799
Incidence	(0, 810)	FISHER'S EXACT, right-sided	0.500	0.875

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

Table of incident by Doses					
incident	Doses				
Frequency Col Pct	0	100	300	1000	Total
Total	47	46	50	45	188

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