Glyphosate Cancer Risks and Failures of the Pesticide Regulatory Process

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11 October, 2017

Brussels, Belgium

Disclosures

- The opinions expressed here and the analyses done to support those opinions are mine alone.
- I am a consultant for a group of US law firms involved in glyphosate litigation.
- I work part-time as a Senior Contributing Scientist for the Environmental Defense Fund (EDF)
  - On issues related to air pollution, biomonitoring, climate change and public health
  - No work on glyphosate

Take Home Messages

1. The current process for reviewing pesticides is scientifically flawed
2. It is time to have an independent, blue-ribbon panels of scientists evaluate the way in which the science is reviewed
3. The regulatory agencies must independently evaluate the raw data to avoid any possible bias in the presentation of the results

Scientific Evidence for Glyphosate Carcinogenicity

- Human epidemiology
- Experimental cancer bioassays in rodents
- Studies of mechanistic endpoints

Cancer Bioassays

- Control all aspects of rodent's environment
- Expose groups of animals to 3 or 4 different doses of glyphosate
- 50 or so animals per group placed at random
- Examine most tissues for cancers
- Look for tumors that increase with increasing dose

Twelve Useful Bioassays

- Rats
  - Sprague-Dawley (4)
    - 3 studies of 24 month duration
    - 1 study of 26 month duration
  - Wistar (3 at 24 months)
- Mice
  - CD-1 Mice (4)
    - 2 studies of 18 month duration
    - 2 studies of 24 month duration
  - Swiss Albino Mice (1 at 24 months)

Recent Evaluations of the Animal Cancer Data

- Renewal Assessment Report (2013)
- Greim et al. (2015)
  - 30 days prior to the IARC monograph meeting
- IARC (2015)
- EFSA/ECHA (2015, 2017)
- US EPA (2016 – draft)

Animal Carcinogenicity Data – Mice 2013 RAR Report

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Study Year	Tumor	2013 RAR
1983	No Tumors	
1993	No Tumors	
1997	No Tumors	
2001	Malignant Lymphomas (M)	X
2009	Malignant Lymphomas (M)	X

Animal Carcinogenicity Data – Mice Add Greim, 2015

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Study Year	Tumor	2013 RAR	Greim, 2015
1983	Kidney Carcinoma (M)		X
	Kidney Aden. and Carc. (M)		X
1993	No Tumors		
1997	Malignant Lymphoma (M)		X
2001	Malignant Lymphomas (M)	X	X
2009	Malignant Lymphomas (M)	X	X
	Lung Adenocarcinoma (M)		X

Animal Carcinogenicity Data – Mice Add IARC, 2015

Study Year	Tumor	2013 RAR	Greim, 2015	IARC, 2015
1983	Kidney Carcinoma (M)		X	X
	Kidney Aden. and Carc. (M)		X	X
1993	Hemangiosarcomas (M)			X
1997	Malignant Lymphoma (M)		X	Not Evaluated
2001	Malignant Lymphomas (M)	X	X	
2009	Malignant Lymphomas (M)	X	X	
	Lung Adenocarcinoma (M)		X	

Animal Carcinogenicity Data – Mice
Add EFSA/ECHA

Study Year	Tumor	2013 RAR	Greim, 2015	IARC, 2015	EFSA/ EChA
1983	Kidney Carcinoma (M)		X	X	X
	Kidney Aden. and Carc. (M)		X	X	X
1993	Hemangiosarcomas (M)			X	X
1997	Malignant Lymphoma (M)		X	Not Evaluated	X
	Hemangiosarcoma (M)				X
	Kidney Adenoma (M)				X
2001	Malignant Lymphomas (M)	X	X		X
2009	Malignant Lymphomas (M)	X	X		X
	Lung Adenocarcinoma (M)		X		

Animal Carcinogenicity Data – Mice Add EPA, 2016

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Study Year	Tumor	2013 RAR	Greim, 2015	IARC, 2015	EFSA/ EChA	EPA, 2016
1983	Kidney Carcinoma (M)		X	X	X	X
	Kidney Aden. and Carc. (M)		X	X	X	X
1993	Hemangiosarcomas (M)			X	X	X
1997	Malignant Lymphoma (M)		X	Not Evaluated	X	
	Hemangiosarcoma (M)				X	
	Kidney Adenoma (M)				X	
	Hemangioma (F)					X
2001	Malignant Lymphomas (M)	X	X		X	X
2009	Malignant Lymphomas (M)	X	X		X	X
	Lung Adenocarcinoma (M)		X			X

Animal Carcinogenicity Data – Mice Add Re-Analysis, Portier, 2017

Study Year	Tumor	2013 RAR	Greim, 2015	IARC, 2015	EFSA/E ChA	EPA, 2016	Portier, 2017
1983	Kidney Carcinoma (M)		X	X	X	X	X
	Kidney Aden. and Carc. (M)		X	X	X	X	X
	Malignant Composite Lymphosarcoma Spleen (F)						X
1993	Hemangiosarcomas (M)			X	X	X	X
1997	Malignant Lymphoma (M)		X	Not Evaluated	X		X
	Hemangiosarcoma (M)				X		X
	Kidney Adenoma (M)				X		X
	Hemangioma (F)					X	X
	Harderian Gland Adenoma (F)						X
2001	Malignant Lymphomas (M)	X	X		X	X	X
	Hemangiomas (F)						X
2009	Malignant Lymphomas (M)	X	X		X	X	X
	Lung Adenocarcinoma (M)		X			X	X

Animal Carcinogenicity Data – Rats
Add Re-Analysis, Portier, 2017

Study Year	Tumor	2013 RAR	Greim, 2015	IARC, 2015	EFSA/ EChA	EPA, 2016	Portier, 2017
1981	Testicular interstitial cell tumors (M)	X	X		X	X	X
	Pancreas Islet Cell Tumors (M)	X		X	X		X
	Thyroid C-Cell Adenomas (F)						X
1990	Pancreas Islet Cell Tumors (M)		X	X	X	X	X
	Hepatocellular adenomas (M)			X	X	X	X
	Hepatocellular Aden. and Carc. (M)			X	X	X	X
	Thyroid C-Cell Adenomas (M)	X	X		X	X	X
	Thyroid C-Cell Aden. and Carc. (M)	X	X		X	X	X
	Thyroid C-Cell Adenomas (F)		X	X	X	X	X
	Adrenal Cortical Carcinoma (F)				X	X	X
1993	Thyroid Follicular Aden. & Carc. (M)						X
	Skin Keratoacanthoma (M)						X
1996	No Tumors			Not Evaluated			
1997	Skin Keratoacanthoma (M)		X				X
	Kidney Adenoma (M)						X
	Basal Cell Carcinoma (M)						X
2001	Hepatocellular Adenoma (M)		X			X	X
2009	Skin Keratocanthoma (M)	X	X				X
	Pituitary Adenoma (M)						X
	Pituitary Adenoma (F)						X
	Mammary Gland Adenocarc. (F)		X			X	X
	Mammary Gland Adenom. and Adenocarc. (F)					X	X

Summary – Mice and Rats

- # tumor findings discussed (34 total)
  - RAR (2013) – 7/34 (21%)
  - Greim (2015) – 15/34 (44%)
  - IARC (2015) – 8/34 (24%)
    - 8 out of 16 possible in studies they reviewed
  - EFSA/EChA – 17/34 (50%)
  - EPA (2016) – 18/34 (53%)
- Ten of these tumor findings have not been discussed in any review

Why is this important?

- Statistically significant findings are sites with potential increases in the rates of tumors as a function of glyphosate exposure
  - These need to be reported for transparency and scientific clarity
- Trusting presentations by industry without verification can lead to bias

Hematopoetic System Tumors

- Humans
  - Non-Hodgkin Lymphoma (NHL)
- Mice
  - Malignant Lymphoma (males)
    - significance in 3 studies, 2 in CD-1 mice
  - Hemangiosarcoma (males)
    - significance in 2 studies
  - Hemangioma (females)
    - significance in 2 studies
  - Malignant Composite Lymphosarcoma of the spleen (1 study in females)

Human versus Mouse

- B- cell lymphomas in humans account for about 85% of NHL cases
- Diffuse large B cell lymphomas are the most common
- B cell lymphomas in mice are part of the class of malignant lymphomas
- Mice are used as a model to study B cell lymphomas in humans
  - Morse et al. (2010) do a very good job of describing how the variants and subtypes of B cell lymphomas in humans match up with the same tumor in mice

Morse, H.C., 3rd, J.M. Ward, and M.A. Teitell, Mouse models of human B lymphoid neoplasms, in The Lymphoid Neoplasms, 2010, CRC Press

EFSA/EChA Reasons for Dismissing Positive Findings for Malignant Lymphomas

- Tumor responses fall within the range of historical rates of tumors in control animals
  - The most appropriate control is the concurrent control.
  - OECD Guideline 116 warns against this approach (see citation to Elmore and Peddada (2009)
  - They suggest using inter-quartile range to avoid unusual responses in controls
  - Using this approach, the responses are outside of the range of the historical controls
- No statistical significance in pairwise tests
  - EPA/IARC - "*Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result*."

EFSA/EChA Reasons for Dismissing Positive Findings for Malignant

- Potential general toxicity at high dose in 1997 study
  - "*No significant differences were noted for mortality between the treated groups and the respective control of either sex*"
  - 7% drop in body weight at high dose associated with a 6% drop in food consumption
  - Thus, there is no indication of toxicity at this high dose; only an indication that the food tastes bad
- The results were only positive in males and not females
  - Not a good criteria for excluding a positive findings
  - Many examples of human carcinogens that are only positive in one sex in rodent studies
    - E.g. 4-Aminobiphenyl (liver cancer and angiosarcoma in males, not females)
    - This is a known human carcinogen

Malignant Lymphomas in Male CD-1 Mice

Study Malignant Lymphoma Male CD-1 Mice		Exposure Groups				p-value trend test
2009 (18-month)	Dose	0	71.4	234.2	810	0.007
	Response	0/51	1/51	2/51	5/51	
1997 (18-month)	Dose	0	165	838.1	4348	0.016
	Response	2/50	2/50	0/50	6/50	
Pooled Analysis – p=0.005 (simple) and p=0.005 (general linear model)						
1983 (24 month)	Dose	0	157	814	4841	0.754
	Response	2/49	5/49	4/49	2/49	
1993 (24 month)	Dose	0	98	297	988.8	0.087
	Response	4/50	2/50	1/50	6/50	
Pooled Analysis – p=0.653 (simple) and p=0.686 (general linear model)						

Take Home Messages

1. The current process for reviewing pesticides is scientifically flawed
2. Create an independent, blue-ribbon panels of scientists evaluate the way in which the science is reviewed
3. Independently evaluate the raw data to avoid any possible bias in the presentation of the results
4. Make public all of the analyses and data to improve transparency and trust

EXTRA SLIDES

Animal Carcinogenicity Data – Rats Add Greim, 2015

Study Year	Tumor	2013 RAR	Greim, 2015
1981	Testicular interstitial cell tumors (M)	X	X
	Pancreas Islet Cell Tumors (M)	X	
1990	Pancreas Islet Cell Tumors (M)		X
	Thyroid C-Cell Adenomas (M)	X	X
	Thyroid C-Cell Aden. and Carc. (M)	X	X
	Thyroid C-Cell Adenomas (F)		X
1993	No Tumors		
1996	No Tumors		
1997	Skin Keratoacanthoma (M)		X
2001	Hepatocellular Adenoma (M)		X
2009	Skin Keratocanthoma (M)	X	X
	Mammary Gland Adenocarc. (F)		X

Animal Carcinogenicity Data – Rats Add IARC, 2015

Study Year	Tumor	2013 RAR	Greim, 2015	IARC, 2015
1981	Testicular interstitial cell tumors (M)	X	X	
	Pancreas Islet Cell Tumors (M)	X		X
1990	Pancreas Islet Cell Tumors (M)		X	X
	Hepatocellular adenomas (M)			X
	Hepatocellular Aden. and Carc. (M)			X
	Thyroid C-Cell Adenomas (M)	X	X	
	Thyroid C-Cell Aden. and Carc. (M)	X	X	
	Thyroid C-Cell Adenomas (F)		X	X
1993	No Tumors			
1996	No Tumors			Not Evaluated
1997	Skin Keratoacanthoma (M)		X	
2001	Hepatocellular Adenoma (M)		X	
2009	Skin Keratocanthoma (M)	X	X	
	Mammary Gland Adenocarc. (F)		X	

Animal Carcinogenicity Data – Rats Add EFSA/EChA

Study Year	Tumor	2013 RAR	Greim, 2015	IARC, 2015	EFSA/ EChA
1981	Testicular interstitial cell tumors (M)	X	X		X
	Pancreas Islet Cell Tumors (M)	X		X	X
1990	Pancreas Islet Cell Tumors (M)		X	X	X
	Hepatocellular adenomas (M)			X	X
	Hepatocellular Aden. and Carc. (M)			X	X
	Thyroid C-Cell Adenomas (M)	X	X		X
	Thyroid C-Cell Aden. and Carc. (M)	X	X		X
	Thyroid C-Cell Adenomas (F)		X	X	X
	Adrenal Cortical Carcinoma (F)				X
1993	No Tumors				
1996	No Tumors			Not Evaluated	
1997	Skin Keratoacanthoma (M)		X		
2001	Hepatocellular Adenoma (M)		X		
2009	Skin Keratocanthoma (M)	X	X		
	Mammary Gland Adenocarc. (F)		X		

Animal Carcinogenicity Data – Rats Add EPA, 2016

Study Year	Tumor	2013 RAR	Greim, 2015	IARC, 2015	EFSA/ EChA	EPA, 2016
1981	Testicular interstitial cell tumors (M)	X	X		X	X
	Pancreas Islet Cell Tumors (M)	X		X	X	
1990	Pancreas Islet Cell Tumors (M)		X	X	X	X
	Hepatocellular adenomas (M)			X	X	X
	Hepatocellular Aden. and Carc. (M)			X	X	X
	Thyroid C-Cell Adenomas (M)	X	X		X	X
	Thyroid C-Cell Aden. and Carc. (M)	X	X		X	X
	Thyroid C-Cell Adenomas (F)		X	X	X	X
	Adrenal Cortical Carcinoma (F)				X	X
1993	No Tumors					
1996	No Tumors			Not Evaluated		
1997	Skin Keratoacanthoma (M)		X			
2001	Hepatocellular Adenoma (M)		X			X
2009	Skin Keratocanthoma (M)	X	X			
	Mammary Gland Adenocarc. (F)		X			X
	Mammary Gland Adenom. & Adenocarc. (F)					X

Animal Carcinogenicity Data – Rats
Add Re-Analysis, Portier, 2017

Study Year	Tumor	2013 RAR	Greim, 2015	IARC, 2015	EFSA/ EChA	EPA, 2016	Portier, 2017
1981	Testicular interstitial cell tumors (M)	X	X		X	X	X
	Pancreas Islet Cell Tumors (M)	X		X	X		X
	Thyroid C-Cell Adenomas (F)						X
1990	Pancreas Islet Cell Tumors (M)		X	X	X	X	X
	Hepatocellular adenomas (M)			X	X	X	X
	Hepatocellular Aden. and Carc. (M)			X	X	X	X
	Thyroid C-Cell Adenomas (M)	X	X		X	X	X
	Thyroid C-Cell Aden. and Carc. (M)	X	X		X	X	X
	Thyroid C-Cell Adenomas (F)		X	X	X	X	X
	Adrenal Cortical Carcinoma (F)				X	X	X
1993	Thyroid Follicular Aden. & Carc. (M)						X
	Skin Keratoacanthoma (M)						X
1996	No Tumors			Not Evaluated			
1997	Skin Keratoacanthoma (M)		X				X
	Kidney Adenoma (M)						X
	Basal Cell Carcinoma (M)						X
2001	Hepatocellular Adenoma (M)		X			X	X
2009	Skin Keratocanthoma (M)	X	X				X
	Pituitary Adenoma (M)						X
	Pituitary Adenoma (F)						X
	Mammary Gland Adenocarc. (F)		X			X	X
	Mammary Gland Adenom. and Adenocarc. (F)					X	X