Evaluating the Carcinogenicity of Glyphosate

Christopher J. Portier, Ph.D.

Is glyphosate safe for health and the environment?

European Parliament, 18 September, 2023

Disclaimer

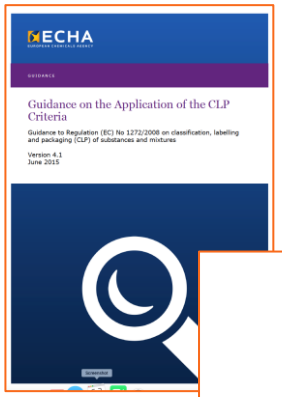
- I have served as an expert witness in trials relating to glyphosate carcinogenicity on behalf of the plaintiffs
- The opinions expressed in this presentation are mine and have not been altered by others in any way

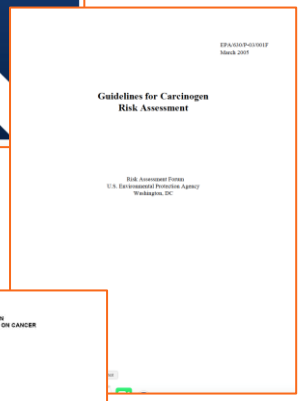
Policy, Process and Science

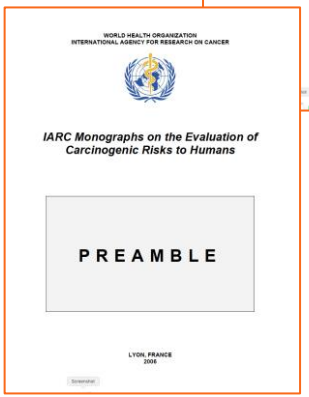
Policy

Process

Science



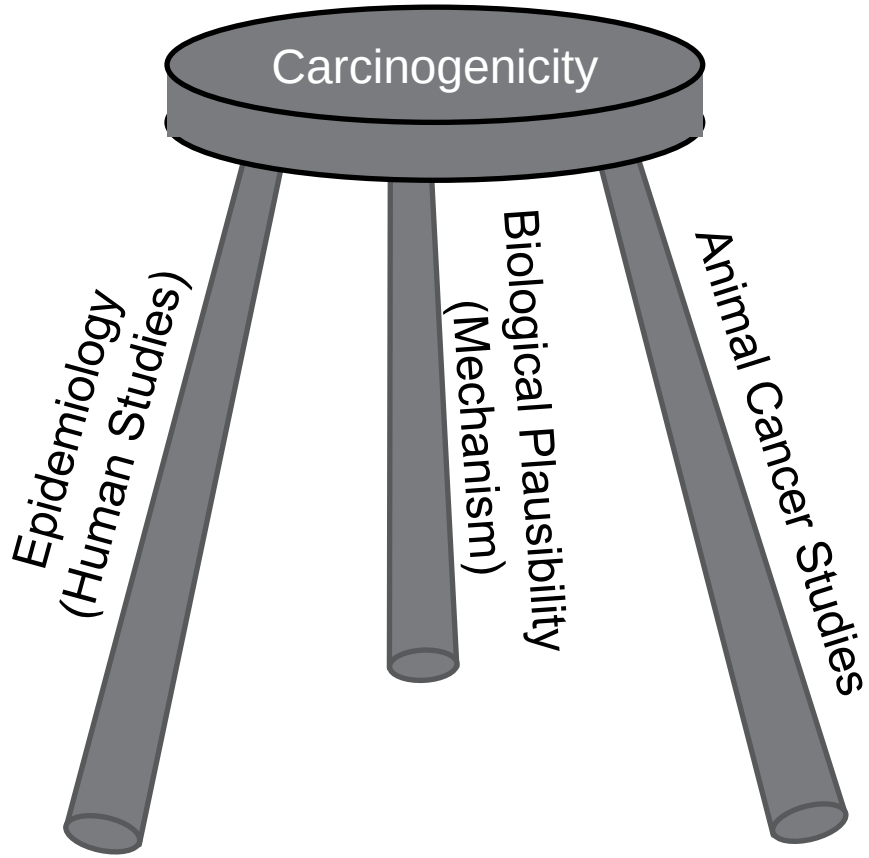




Guidance Documents

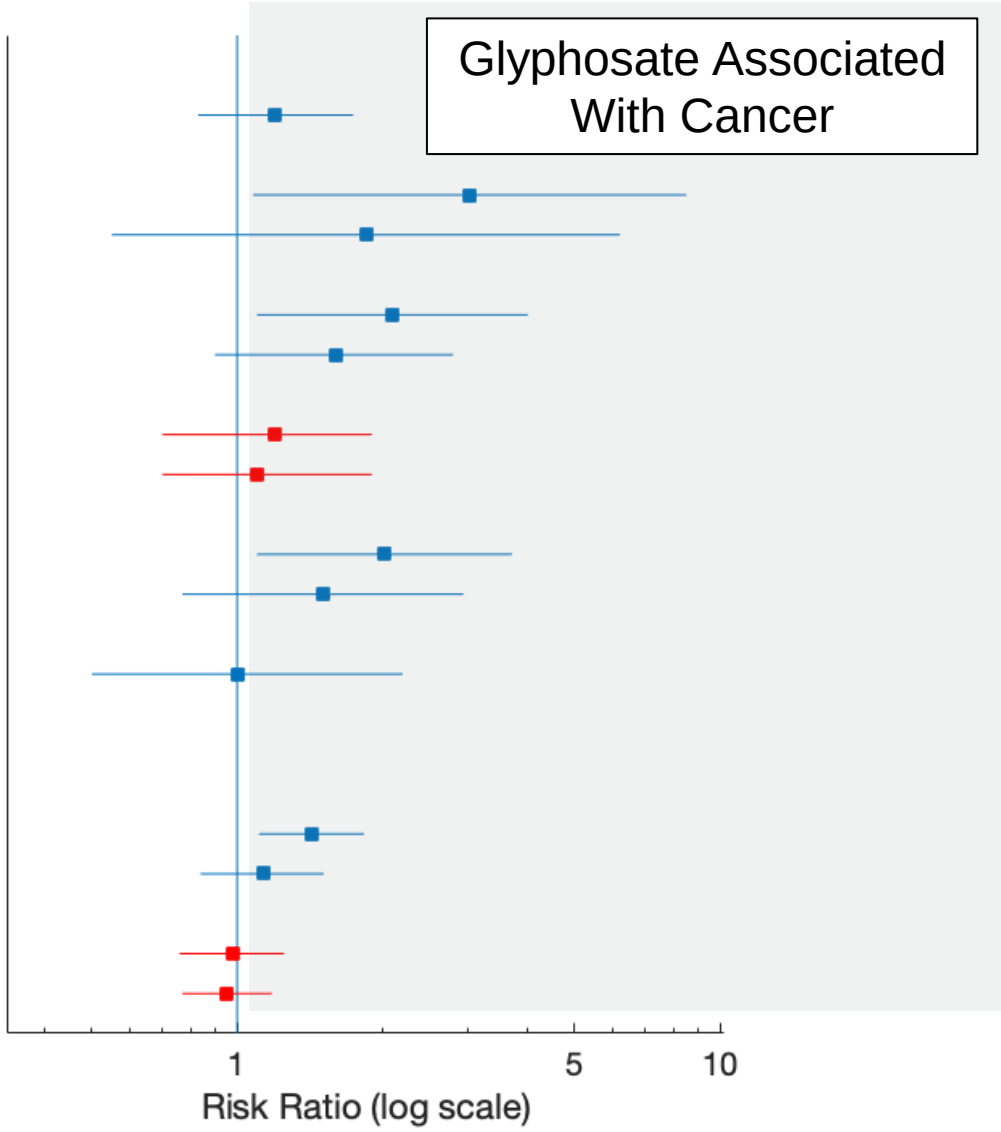
Bradford Hill

Three Key Areas of Review



Plot Summary of Published Epidemiology Studies (Ever vs Never Exposed)

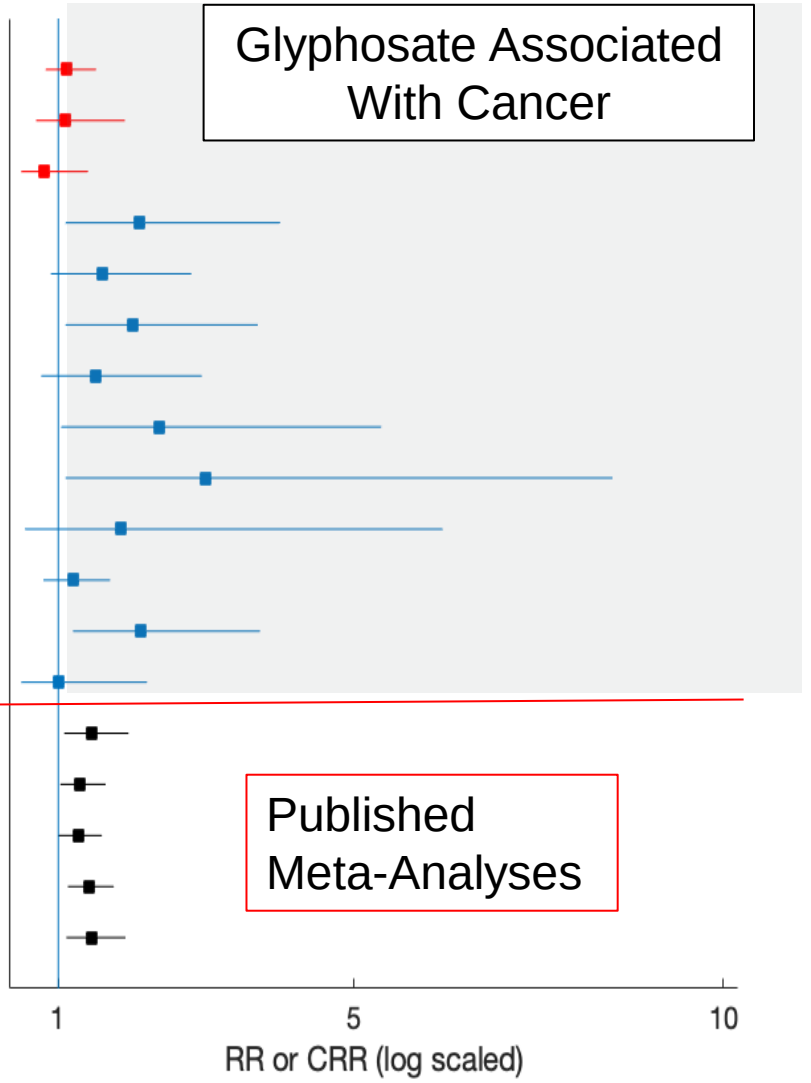
Study	RR	Lower	Upper
McDuffie et al. (2001)			
no pesticide adjustment	1.20	0.83	1.74
Hardell et al. (2002)			
no pesticide adjustment	3.04	1.08	8.52
adjusted for pesticides	1.85	0.55	6.20
De Roos et al. (2003)			
adjusted for pesticides	2.10	1.10	4.00
Bayesian modeling	1.60	0.90	2.80
De Roos et al. (2005)			
no pesticide adjustment	1.20	0.70	1.90
adjusted for pesticides	1.10	0.70	1.90
Eriksson et al., (2008)			
no pesticide adjustment	2.02	1.10	3.71
adjusted for pesticides	1.51	0.77	2.94
Orsi et al. (2009)			
no pesticide adjustment	1.00	0.50	2.20
Andreotti et al. (2018)			
not provided			
Pahwa et al. (2019) NAPP			
no pesticide adjustment	1.43	1.11	1.83
adjusted for pesticides	1.13	0.84	1.51
Leon et al. (2019) AGRICOH			
no pesticide adjustment	0.98	0.76	1.25
adjusted for pesticides	0.95	0.77	1.18



Plot Summary of Published Meta-Analyses

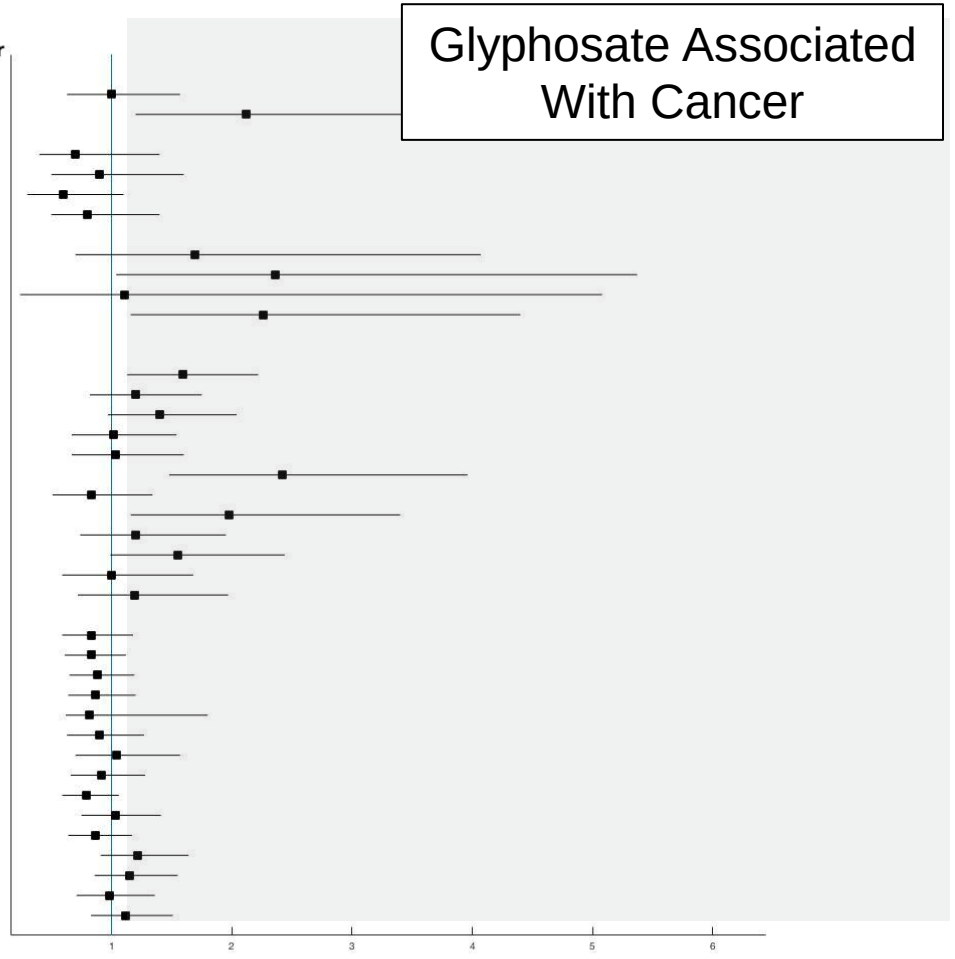
(derived from Zhang et al. (2019), Table 7)

Study	RR	Lower	Upper	Included
A: Andreotti et al. (2018) (highest exposure)	1.12	0.83	1.51	
B: De Roos et al. (2005) (ever/never)	1.10	0.70	1.90	
C: highest exposure	0.80	0.50	1.40	
D: De Roos et al. (2003) (ever/never)	2.10	1.10	4.00	
E: Bayesian regression (ever/never)	1.60	0.90	2.80	
F: Eriksson et al., (2008) (ever/never)	2.00	1.10	3.70	
G: most adjusted (ever/never)	1.51	0.77	2.94	
H: > 10 days	2.36	1.04	5.37	
I: Hardell and Eriksson (1999) (ever/never)	3.00	1.10	8.50	
J: most adjusted (ever/never)	1.85	0.55	6.20	
K: McDuffie et al. (2001) (ever/never)	1.20	0.80	1.70	
L: > 2 days/year	2.12	1.20	3.73	
M: Orsi et al. (2009) (ever/never)	1.00	0.50	2.20	
Schinasi and Leon (2014)	1.45	1.08	1.95	B,D,F,I,K,M
IARC (2015)	1.30	1.03	1.64	B,D,G,J,K,M
Chang and Delzel (2016) (Model1)	1.27	1.01	1.59	B,E,G,J,K,M
Zhang et al. (2019) (use Andreotti et al. (2018)	1.41	1.13	1.75	A,D,H,J,L,M
Use De Roos et al.(2005)	1.45	1.11	1.91	C,D,H,J,L,M



Exposure-Time-Response Summary Plot

Study	RR	Lower	Upper
McDuffie et al. (2001)			
>0 and <2 days/year	1.00	0.63	1.57
>2 days/year	2.12	1.20	3.73
De Roos et al. (2005)			
tertile 2 cumulative exposure	0.70	0.40	1.40
tertile 3 cumulative exposure	0.90	0.50	1.60
tertile 2 intensity exposure	0.60	0.30	1.10
tertile 3 intensity exposure	0.80	0.50	1.40
Eriksson et al., (2008)			
<10 days exposure	1.69	0.70	4.07
>10 days exposure	2.36	1.04	5.37
1-10 year latency	1.11	0.24	5.08
>10 year latency	2.26	1.16	4.40
NAPP - Canada			
0-3.5 years - unadj	1.59	1.13	2.22
>3.5 years - unadj	1.20	0.82	1.75
0-3.5 years - adju	1.40	0.97	2.04
>3.5 years - adj	1.02	0.67	1.54
>0 and <2 days/year - unadj	1.03	0.67	1.60
>2 days/year - unadj	2.42	1.48	3.96
>0 and <2 days/year - adj	0.83	0.51	1.34
>2 days/year - adj	1.98	1.16	3.40
<7 days exposure - unadj	1.20	0.74	1.95
>7 days exposure - unadj	1.55	0.99	2.44
<7 days exposure - adj	1.00	0.59	1.68
>7 days exposure - adj	1.19	0.72	1.97
Andreotti et al. (2018)			
Q1 intensity	0.83	0.59	1.18
Q2 intensity	0.83	0.61	1.12
Q3 intensity	0.88	0.65	1.19
Q4 intensity	0.87	0.64	1.20
Q4 intensity - enrollment only	0.82	0.62	1.80
Q4 intensity - both studies	0.90	0.63	1.27
Q4 intensity - 2005 follow-up	1.04	0.70	1.57
Q1 intensity - 5 year lag	0.92	0.66	1.28
Q2 intensity - 5 year lag	0.79	0.59	1.06
Q3 intensity - 5 year lag	1.03	0.75	1.41
Q4 intensity - 5 year lag	0.87	0.64	1.17
Q1 intensity - 20 year lag	1.22	0.91	1.64
Q2 intensity - 20 year lag	1.15	0.86	1.55
Q3 intensity - 20 year lag	0.98	0.71	1.36
Q4 intensity - 20 year lag	1.12	0.83	1.51



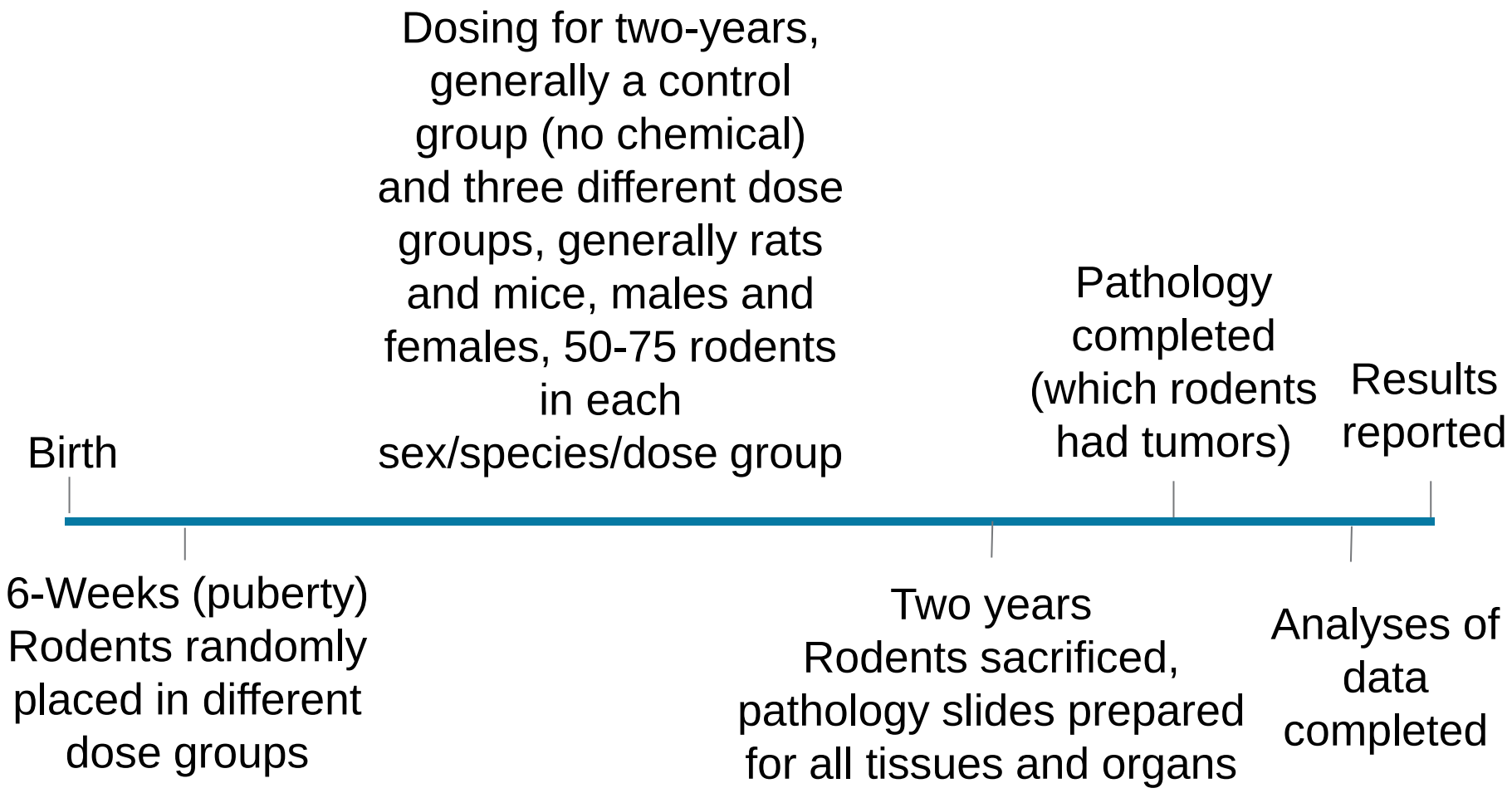
Exposure Missclassification in Andreotti et al. (2018)

- About 1/3 of the participants in Andreotti et al. (2018) did not respond to the questionnaire and their exposures were “imputed” using a failed statistical model
- The accuracy of their predictions is 55.7%
  - Randomly assigning exposure would give you 50% accuracy
- This misclassification reduces the risk estimate, potentially to below zero
- This study should be given little or no weight in the evaluation

Evaluation: Epidemiology

- Positive association exists between glyphosate formulation use and Non-Hodgkins Lymphoma (NHL)
- Causal inference is credible
- Cannot rule out chance, bias, confounding, exposure misclassification
  - Depends on the study
- ECHA CLP Designation for the epidemiology alone would be “Limited Evidence of Carcinogenicity”
  - This should automatically result in at least a classification of 2 in the CLP

Two-Year Carcinogenicity Study



Animal Cancer Studies

- The analyses of the individual studies
  - Quality
  - Increased cancer risks with increased dose
  - Supporting evidence like changes that precede cancer
- Consistency across studies
  - Pooled or meta-analyses
- Historical evidence
- Mechanistic evidence
- Any other associated scientific literature.

Summary of level of evidence[1] for tumors observed to have a significant trend in 13 rodent carcinogenicity studies in male and female, mice and rats.[2]

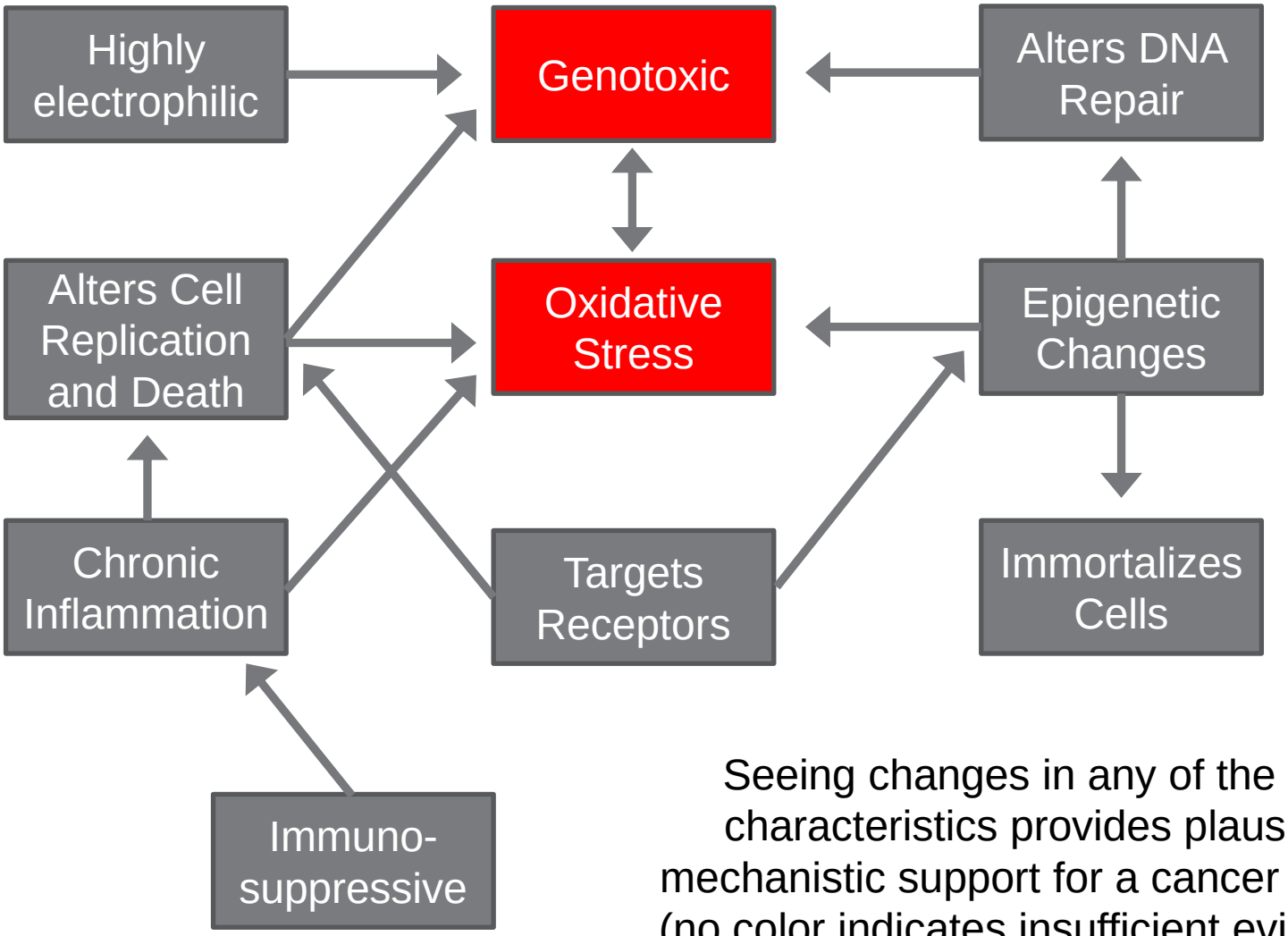
Tumor	Males				Females			
	SD Rat	Wistar Rat	CD-1 Mouse	Swiss Mouse	SD Rat	Wistar Rat	CD-1 Mouse	Swiss albino mouse
Adrenal cortical carcinoma					CE			
Alviolar-Bronchiolar tumor			NE				NE	
Harderian gland tumor							NE	
Hemangioma							CE	CE
Hemangiosarcomas			CE					
Kidney tumor	CE		CE	SE				EE
Liver Adenoma	SE	CE						
Mammary tumor						SE		
Malignant lymphoma			CE	SE			CE	
Pancreas Islet Cell Tumor	SE							
Pituitary tumor		SE				SE		
Skin basal-cell tumor	CE							
Skin keratoacanthoma	CE	CE						
Thyroid C-cell tumor	EE				EE			
Thyroid follicular-cell tumor	EE							
Testis interstitial-cell Tumor	SE							

1 – CE=clear evidence; SE=some evidence; EE=equivocal evidence; NE=no evidence

Evaluation: Animal Cancer Data

- Positive association exists between glyphosate dose and an increase in carcinogenicity in two or more independent cancer studies in animals
- Causal inference is credible
- ECHA CLP Designation for the animal cancer data alone would be “Sufficient Evidence of Carcinogenicity”
  - This should automatically result in at least a classification of 1B in the CLP

Ten Key Characteristics of Cancer
(Smith et al., 2016)



Seeing changes in any of the key characteristics provides plausible mechanistic support for a cancer finding (no color indicates insufficient evidence)

Is glyphosate safe for health and the environment?

- No.
- It can cause cancer in humans.
- It should be in CLP category 1B;

presumed to have carcinogenic potential for humans, classification is largely based on animal evidence

Main Characteristics of Science

- Objective
  - Accept facts as they are
- Verifiable/Testable
  - Based on facts, not faith or dogma
- Ethically Neutral
  - How it will be used does not alter how it is done
    - e.g. Transparency on issues like authors, funding sources, and conflicts of interest
- Systematic
  - Hypothesize, experiment, analyze, conclude, repeat
- Reliable
  - Replicable under prescribed circumstances
- Specific
  - Clear and precise
- Accurate
  - Correctness of statements
- Tentative
  - Subject to change with new facts
- Able to explain and predict