Pesticides

How to evaluate the scientific literature for cancer risks

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Solothurn

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

Five Basic Steps of Human Health Risk Assessment

- What exposure should we evaluate?
- What information is available for the evaluation?
- How do we choose from this information what is informative?
- Is this exposure a hazard?
- How big is the hazard relative to the exposure?

Gohlke and Portier (2006)

Bradford Hill Criteria (1965) [1]

- Consistency of the observed association.
  - A pattern of elevated risks is observed across several independent studies
  - The reproducibility of findings constitutes one of the strongest arguments for causality.
- Strength of the observed association.
  - Large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors.
  - A modest risk does not preclude a causal association and may reflect a lower level of exposure, an agent of lower potency, or a common disease with a high background level.

[1] modified from USEPA Cancer Guidelines (2005)

Bradford Hill Criteria (1965) [1]

- Specificity of the observed association.
  - One cause is associated with a single effect or disease (Hill, 1965).
    - e.g. lung mesothelioma and asbestos
  - Many agents cause cancer at multiple sites, and many cancers have multiple causes
    - the presence of specificity may support causality, its absence does not exclude it
- Temporal relationship of the observed association.
  - Exposure is known to precede development of the disease (epidemiology)
  - Because a latent period of up to 20 years or longer is often associated with cancer development in adults, the study should consider whether exposures occurred sufficiently long ago to produce an effect at the time the cancer is assessed
  - This is among the strongest criteria for an inference of causality.

[1] modified from USEPA Cancer Guidelines (2005)

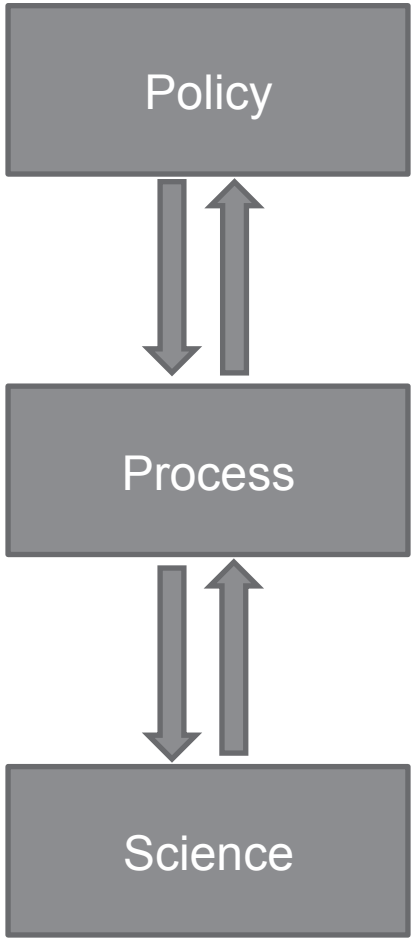
Bradford Hill Criteria (1965) [1]

- Biological gradient (exposure-response relationship).
  - A clear exposure-response relationship
    - e.g., increasing effects associated with greater exposure
  - This pertains to epidemiology and toxicology
  - There are many possible reasons that an epidemiologic study may fail to detect an exposure-response relationship
- Biological plausibility.
  - Data exists from experimental studies or other sources demonstrating plausible biological mechanisms
  - A lack of a biological mechanism is not a reason to reject causality
- Coherence.
  - Information is consistent from epidemiology, animal bioassays, and short-term studies

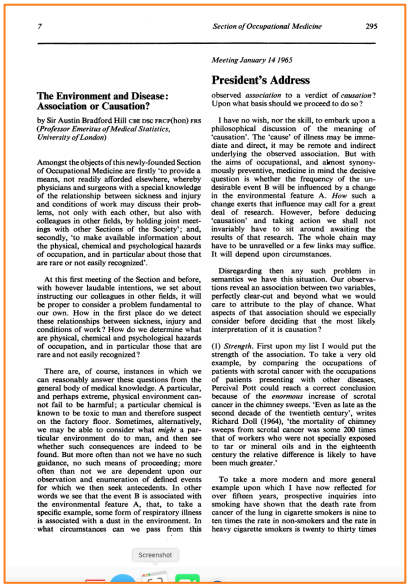
Bradford Hill Criteria (1965) [1]

- Experimental evidence (from human populations).
  - A change in exposure brings about a change in disease frequency in a controlled experiment in humans
    - e.g. the the risk of lung cancer decreases following cessation of smoking.
  - Experimental evidence is seldom available from human populations and exists only when conditions of human exposure have occurred to create a “natural experiment” at different levels of exposure.
- Analogy.
  - Chemicals with similar structures, mechanisms and properties exist that are already known the cause cancer

Policy, Process and Science

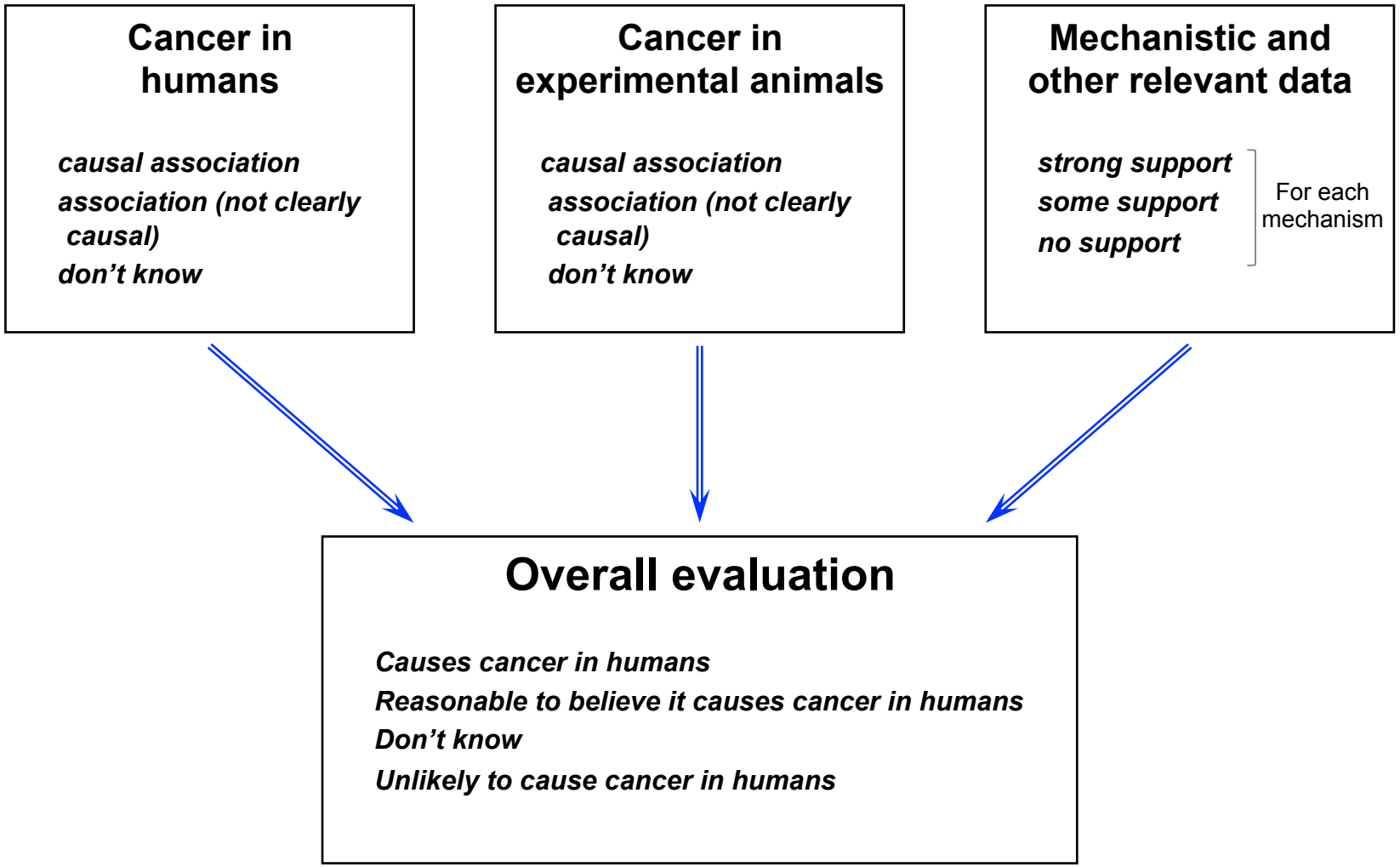


Guidance Documents



Bradford Hill

Combining human evidence, animal evidence, and mechanistic evidence



Human Data: Sufficient Evidence of Carcinogenicity

- ECHA: a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence
- IARC: the same

Human Data: Limited Evidence of Carcinogenicity

- ECHA: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.
- IARC: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

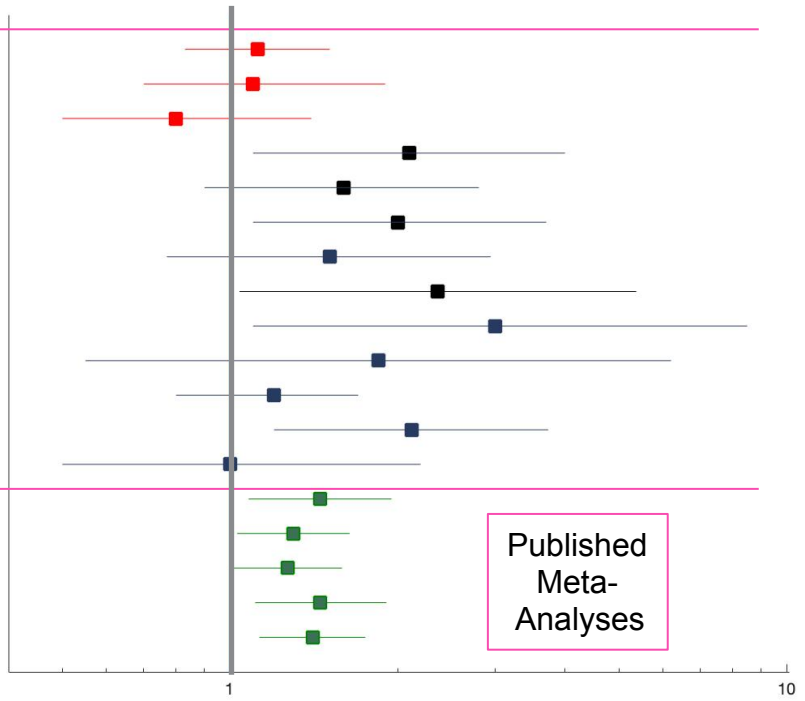
Glyphosate - Background

- Broad-spectrum, non-selective herbicide
- First synthesized by Cilag (1950) as a possible drug
- Re-synthesized by Monsanto (1970)
- Patent expired [1991, 2000 (US)]
- Hundreds of trade names
- Approximately 91 producers in 20 countries
- Believed to be the most heavily used herbicide in the world

Plot Summary of Published Meta-Analyses

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

Study	RR	Lower	Upper	Included
A: Andreotti et al. (2018)	1.12	0.83	1.51	
B: De Roos et al. (2005)	1.10	0.70	1.90	
C: highest exposure	0.80	0.50	1.40	
D: De Roos et al. (2003)	2.10	1.10	4.00	
E: Bayesian regression	1.60	0.90	2.80	
F: Eriksson et al., (2008)	2.00	1.10	3.70	
G: most adjusted	1.51	0.77	2.94	
H: > 10 days	2.36	1.04	5.37	
I: Hardell and Eriksson (1999)	3.00	1.10	8.50	
J: most adjusted	1.85	0.55	6.20	
K: McDuffie et al. (2001)	1.20	0.80	1.70	
L: > 2 days/year	2.12	1.20	3.73	
M: Orsi et al. (2009)	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)	1.27	1.01	1.59	B,E,G,J,K,M
Zhang et al. (2019)	1.45	1.11	1.91	C,D,H,J,L,M
Use De Roos et al.(2005)	1.41	1.13	1.75	A,D,H,J,L,M



Human Data Conclusions

EFSA – very limited?

From the wealth of epidemiological studies, the majority of experts concluded that there is very limited evidence for an association between glyphosate-based formulations and non-Hodgkin lymphoma, overall inconclusive for a causal or clear associative relationship between glyphosate and cancer in human studies. Minority views nevertheless were expressed that there was either inadequate or limited evidence of an association. No evidence of carcinogenicity was confirmed by the large

IARC Working Group – limited evidence

There is *limited evidence* in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin lymphoma.

Animal Data: Sufficient Evidence in Animals

- ECHA
  - a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites
- IARC – exactly the same

Animal Data: Limited Evidence in Animals

- EChA
  - the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.
- IARC – exactly the same

Tumor Findings in Wistar Rats

Tumor	Study			Pooled Analysis*
	Suresh	Brammer	Wood	GLM
Hepatocellular Adenomas (male)	0.374	0.008	0.418	0.030
				[0.015]
Mammary Gland Adenomas and Carcinomas (female)	0.970	0.575	0.007	0.258
				[0.027]
Skin Keratoacanthoma (male)	1	0.392	0.030	0.033
				[0.033]
Pituitary Adenoma (male)	0.376	0.922	0.045	0.454
				[0.476]
Pituitary Adenoma (female)	0.967	0.291	0.014	0.123
				[0.029]

* - p-values in square brackets [p] evaluate the sensitivity of the p-values to the exclusion of Suresh (1996) from the pooling

Tumor Findings in Sprague-Dawley Rat

Tumor	Study				Pooled Analysis
	Lankas	Stout & Ruecker	Atkinson	Enemoto	GLM*
Hepatocellular Adenomas (male)	0.630	0.015	0.155	0.371	0.012
					[0.012]
Kidney Adenomas (male)	0.979	0.813	1	0.004	0.042
					[0.038]
Adrenal Cortical Carcinomas (female)	0.851	0.015	0.434	1	0.984
					[0.027]
Skin Keratoacanthoma (male)	1	0.078	0.047	0.029	<0.001
					[0.002]
Basal Cell Tumors (male)	0.251	0.250	1	0.015	0.020
					[0.021]

* - p-values in square brackets [p] evaluate the sensitivity of the p-values to the exclusion of Lankas (1981) from the pooling

Tumor Findings in Sprague-Dawley Rats (continued)

Tumor	Study				Pooled Analysis
	Lankas	Stout & Ruecker	Atkinson	Enemoto	GLM*
Testicular Interstitial Cell Tumors (male)	0.009	0.296	0.580	0.594	0.461 [0.480]
Thyroid C-Cell Adenomas and Carcinomas (female)	0.122	0.052	0.197	0.692	0.145 [0.151]
Thyroid C-Cell Adenomas and Carcinomas (male)	0.072	0.068	0.183	0.697	0.181 [0.176]
Thyroid Follicular-Cell Adenomas and Carcinomas (male)	0.748	0.225	0.034	0.990	0.228 [0.234]
Pancreatic Islet-Cell Tumors (male)	0.312	0.147	0.200	0.844	0.260 [0.263]

* - p-values in square brackets [p] evaluate the sensitivity of the p-values to the exclusion of Lankas (1981) from the pooling

Tumor Findings in CD-1 Mice

Tumor	Study*				Pooled Analysis	
	Knezevich & Hogan	Atkinson	Sugimoto	Wood	Mo.	GLM
Hemangiosarcoma (male)	0.503	0.004	0.200	1	18	<0.001[a]
	[0.591]	[0.001]	[0.004]		24	0.087[a]
					all	0.033
Kidney Adenoma and Carcinoma (male)	0.065	1	0.062	1	18	<0.001[a]
	[0.011]		[0.005]		24	0.075
					all	0.013
Malignant Lymphoma (male)	0.754	0.087	0.016	0.007	18	0.005
					24	0.686
					all	0.093

* - p-values in square brackets [p] use historical controls from Giknis and Clifford (2000):
[a] – using simple linear model instead of logistic regression due to intercept problems

Animal Carcinogenicity Data – Mice

Study Year	Tumor	2013 RAR	Greim, 2015	IARC, 2015	EFSA/ EChA	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

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 Carcinoma (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 Adenoma (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
	Pituitary Adenoma and Carcinoma (F)						X
	Mammary Gland Adenocarc. (F)		X			X	X
	Mammary Gland Adenom. and Adenocarc. (F)					X	X

Conclusions

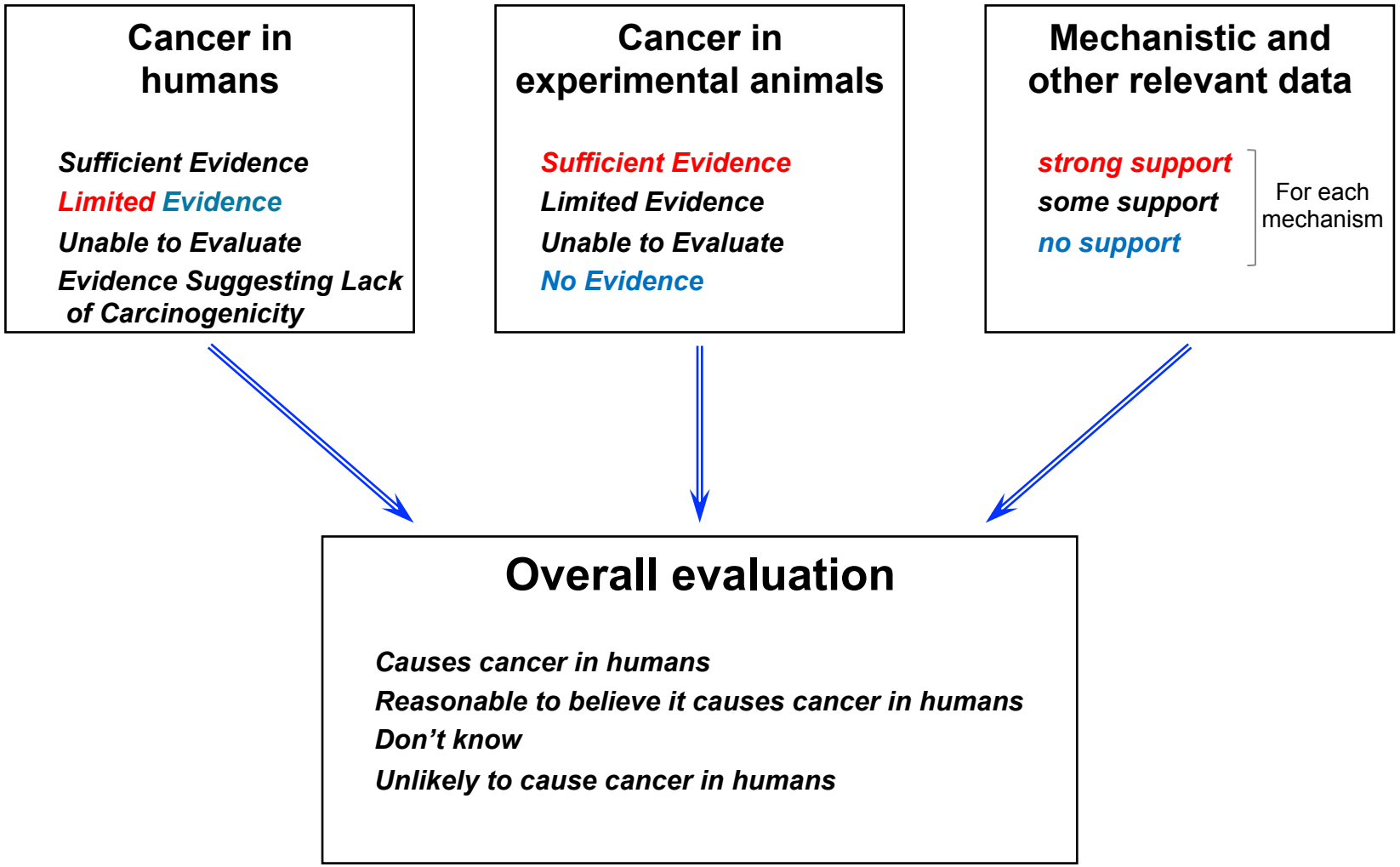
EFSA

No evidence of carcinogenicity was confirmed by the large majority of the experts (with the exception of one minority view) in either rats or mice due to a lack of statistical significance in pair-wise comparison tests, lack of consistency in multiple animal studies and slightly increased incidences only at dose levels at or above the limit dose/MTD, lack of pre-neoplastic lesions and/or being within historical control range. The statistical significance found in trend analysis (but not in pair-wise comparison) *per se* was balanced against the former considerations.

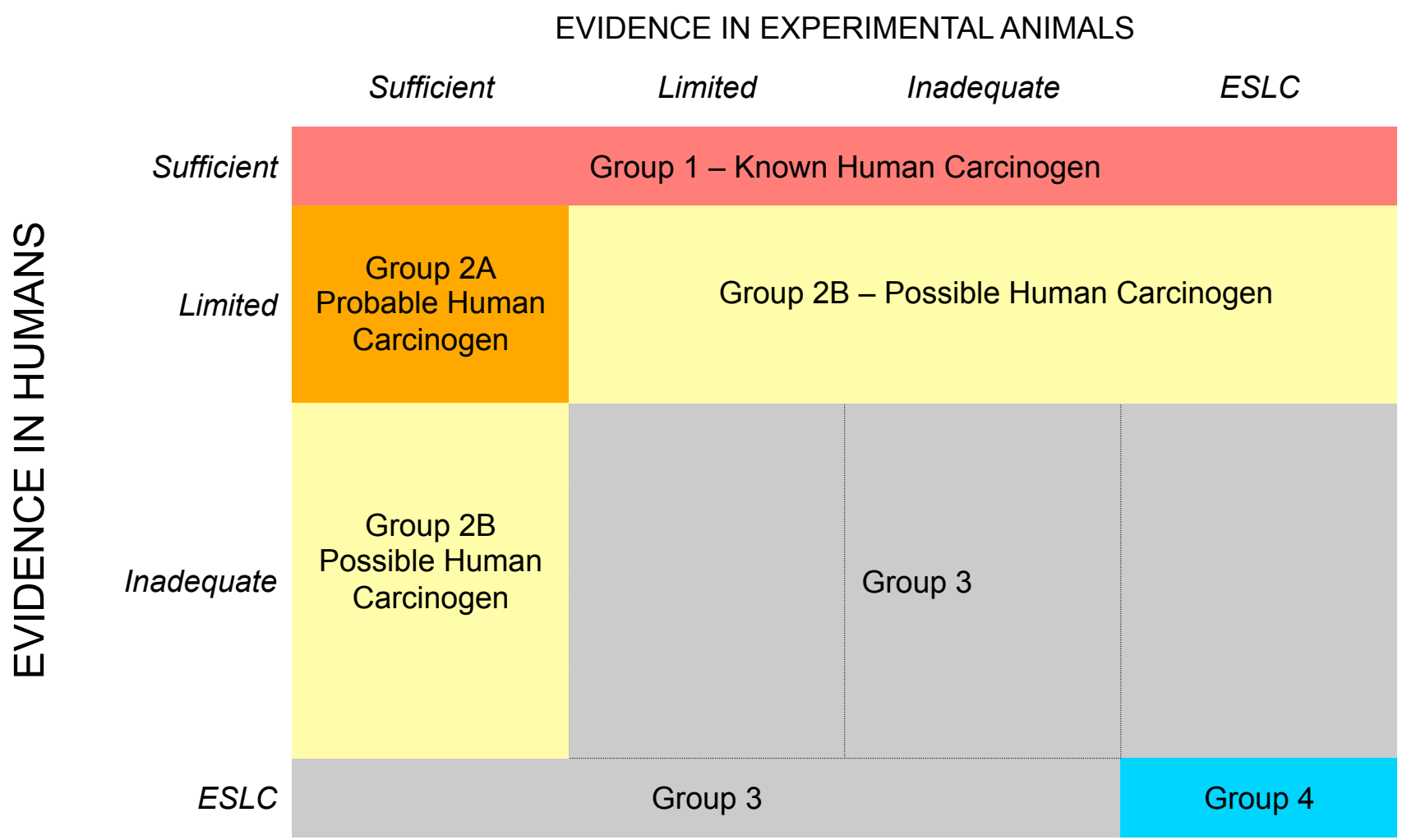
IARC Working Group

There is *sufficient evidence* in experimental animals for the carcinogenicity of glyphosate.

Combining human evidence, animal evidence, and mechanistic evidence

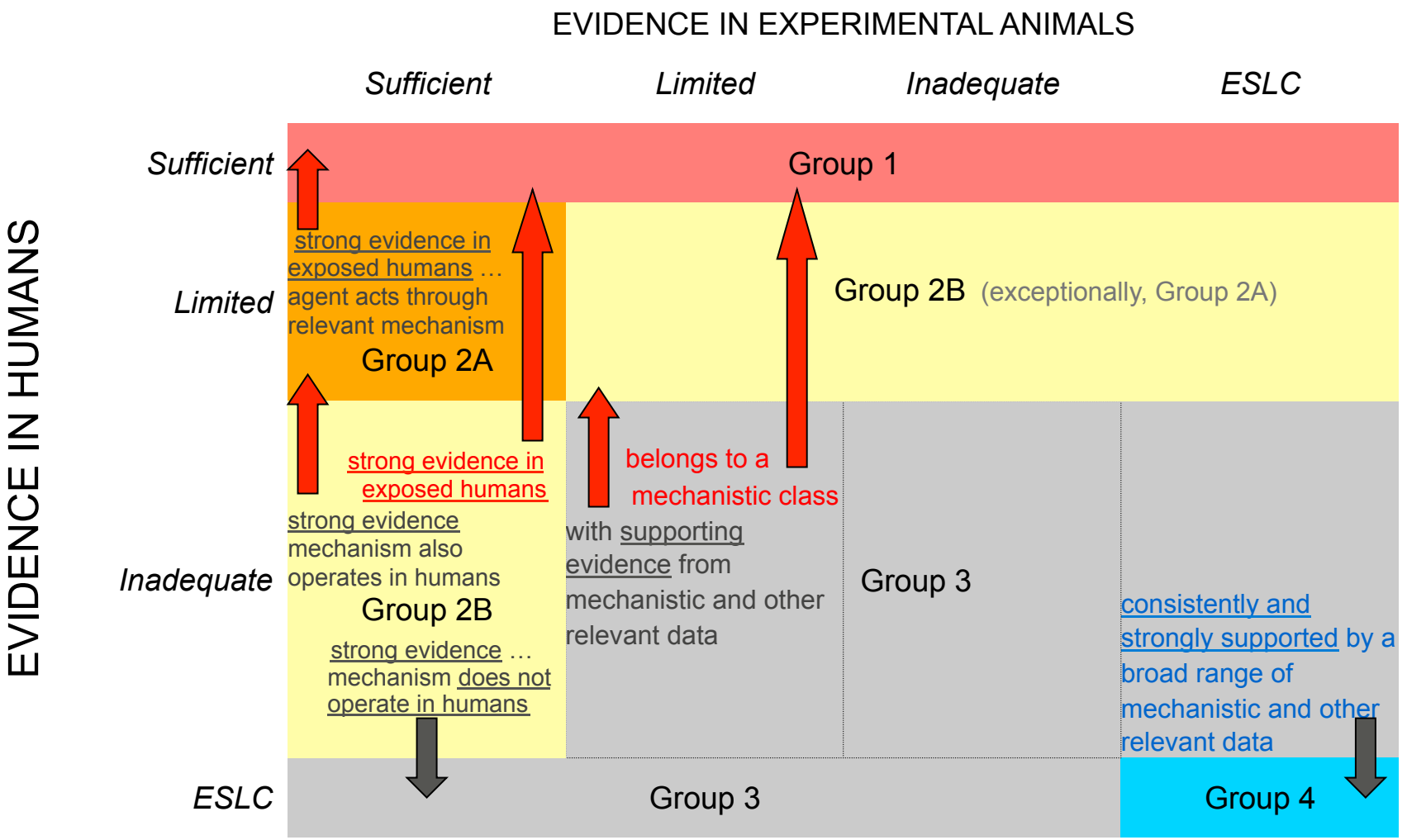


IARC Overall Evaluation



Modified from Vincent Cogliano, IARC

IARC Overall Evaluation



Modified from Vincent Cogliano, IARC

CLP Guidance on Carcinogenicity

- Category 1: Known or presumed human carcinogens
  - Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence
  - Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence

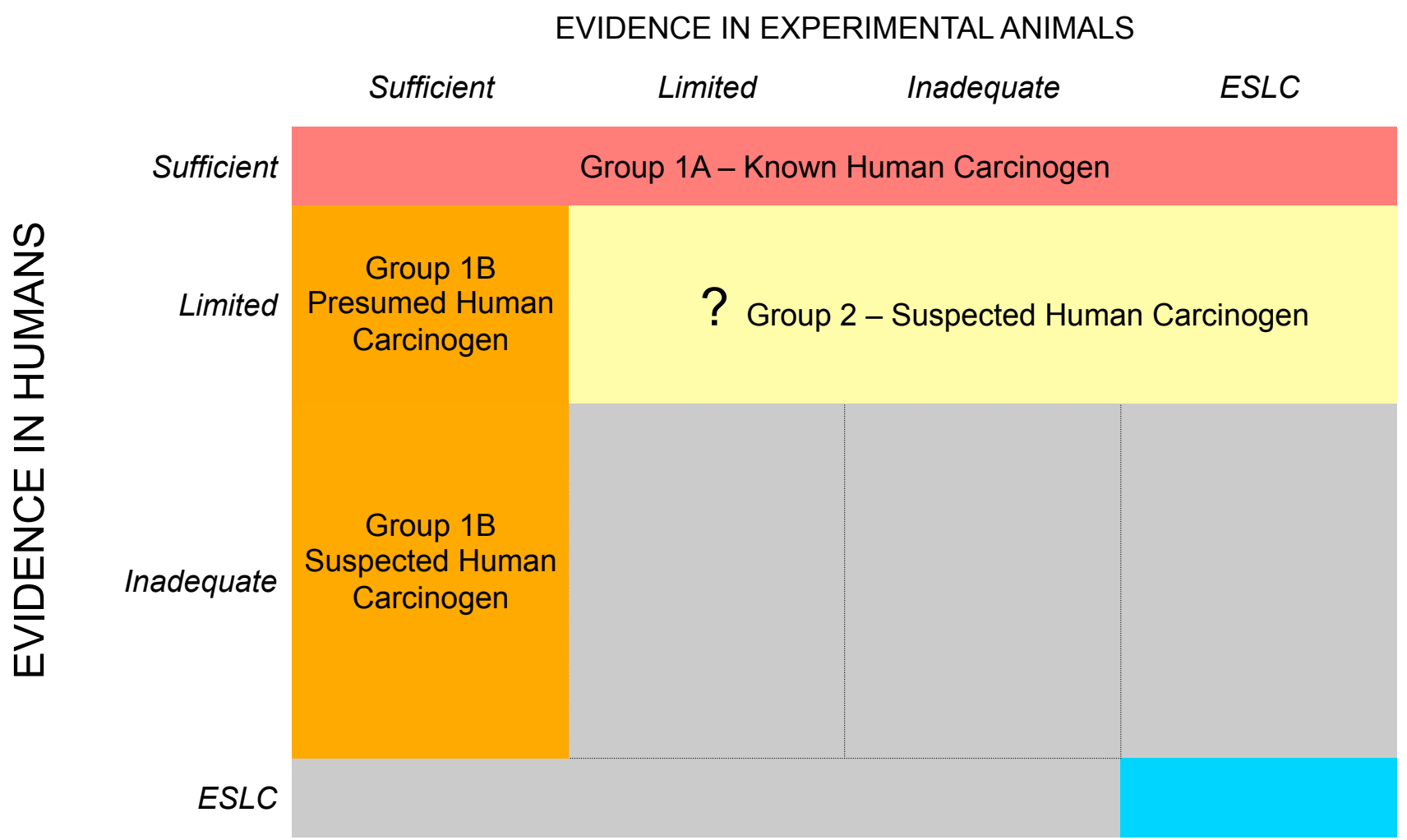
Guidance on the Application of the CLP Criteria, ECHA (2015)

CLP Guidance on Carcinogenicity
(continued)

- The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from:
  - human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or
  - animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen).
- In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals

Guidance on the Application of the CLP Criteria, ECHA (2015)

ECHA Overall Evaluation



Modified from Vincent Cogliano, IARC

Conclusions on Glyphosate

EFSA: glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential according to Regulation (EC) No 1272/2008

IARC: Glyphosate is *probably carcinogenic to humans (Group 2A)*

USEPA: The strongest support is for "not likely to be carcinogenic to humans"