

Carcinogenicity of Glyphosate and the “Weight of Evidence Approach”

Peter Clausing,
PAN Germany

CLP Legislation 1272/2008

Carcinogen 1B (sufficient evidence)

- increased incidence of malignant neoplasms in **two or more studies** in one species

Carcinogen 2 (limited evidence)

- evidence restricted to a **single experiment**
- **unresolved questions** (design, conduct or interpretation of the studies)
- only **benign neoplasms**
- carcinogenicity restricted to tumor promoting activity

Statistical methods

Entity	EU - originally	IARC
Kind of test	Pairwise	Trend
Test statistic	Two-tailed	One-tailed



weak



powerful



OECD Guidance 116:

- Trend tests recommended
- Significance in either kind of test sufficient
- One-tailed may be more appropriate

RAR as of 03/2015 (**pairwise, two-tailed**):
Conclusion: „no carcinogenic hazard“

Study	Malignant Lymphoma	Renal tumors	Haemangio-sarcoma
1983	-	-	-
1993	-	-	-
1997	-	-	-
2001	+	-	-
2009	-	-	-

Statistical methods

Entity	BfR (August 2015)	IARC
Kind of test	Pairwise Trend	Trend
Test statistic	Two-tailed	One-tailed



(weak)



powerful

→ **Significance in either kind of test is sufficient**

Addendum to RAR, **trend test, two-tailed**)

Study	Malignant Lymphoma	Renal carcinoma	Haemangio-sarcoma
1983	-	+	-
1993	-	-	+
1997	+	+	+
2001	- (pw: +)	+	-
2009	+	-	-

(pairwise / trend tests, two-tailed)
Conclusion: „no carcinogenic hazard“

HDE = High Dose Effect

Study		Malignant Lymphoma	Renal tumors	Haemangio-sarcoma
1983	HDE	-	- / +	-
1993		-	-	- / +
1997	HDE	- / +	- / +	- / +
2001	Virus	+ / -	- / +	-
2009		- / +	-	-

The suspected virus infection

- **EFSA Conclusion - November 2015:**

“The study was re-considered during the second experts’ teleconference (TC 117) **as not acceptable due to viral infections** that could influence survival as well as tumour incidence – especially lymphomas.”

- **ECHA Draft CLH Report 2016**

During a **teleconference** ... it was

mentioned by an U.S. EPA observer

that the study had been excluded due to the occurrence of viral infection However, **the actual basis** of EPA’s decision is **not known**.

pairwise / trend tests, one-tailed

Conclusion: ???

Study	Malignant Lymphoma	Renal tumors	Haemangio-sarcoma
1983 HDE	-	- / +	-
1993	invalid	-	+ / +
1997 HDE	- / +	- / +	- / +
2001	+ / +	- / +	-
2009	+ / +	-	-

pairwise / trend tests, one-tailed

Study	Malignant Lymphoma
1983 HDE	-
1993	invalid
1997 HDE	- / +
2001	+ / +
2009	+ / +

Authorities' main Arguments:

- lack of significance in pair-wise comparison
- lack of consistency in multiple animal studies
- Only seen at very high doses
-
- Conclusion (**not!**) covered by historical control data

CLP Legislation 1272/2008

Carcinogen 1B (sufficient evidence):

- Tumor increase in two or more studies

Glyphosate:

- 3 studies with significant ↑ in the same tumor type
- 2 of the with a clearly Increase dose-dependent
(10-15-16-19; 0-1-2-5)
- Top doses (mg/kg): 1460 810

What was driving the decision for not even using Category 2 ?

Backup slides

Statistics

(**pairwise comparison** vs. trend test,)

Group	Incidence
Control	0
Low dose	1
Mid dose	3
High dose	6

Trend test

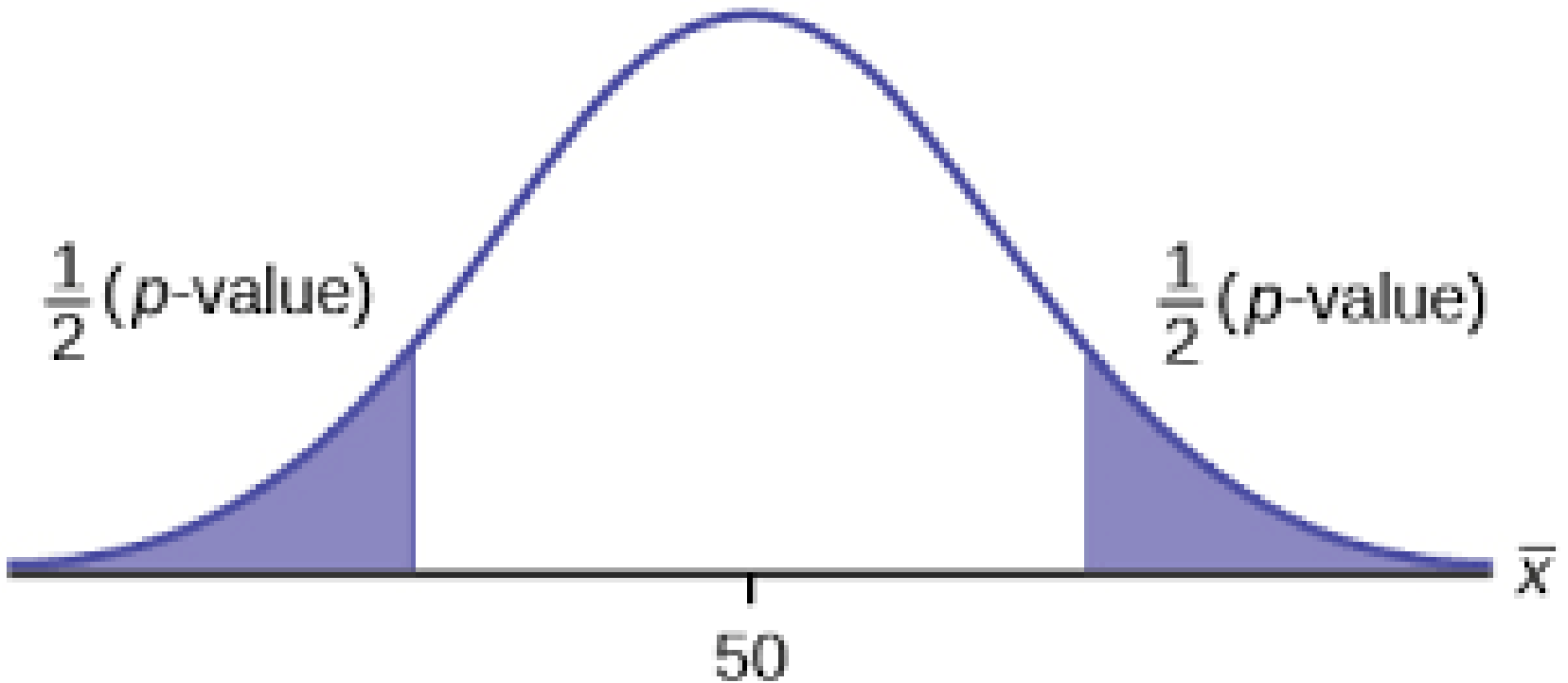


Pairwise comparison

The diagram features a large black bracket on the right side of the table, spanning the four rows (Control, Low dose, Mid dose, High dose). Two red arrows originate from the right side of this bracket. One arrow points from the top of the bracket (Control) to the text 'Pairwise comparison'. The other arrow points from the bottom of the bracket (High dose) to the same text. This visualizes the concept of pairwise comparison between the highest and lowest incidence groups.

Statistics

(one-tailed vs. two-tailed)



**OECD Guidance 116 recommends
One-tailed Tests**