Hazard Assessment of Glyphosate Carcinogenicity and Reproductive Toxicity

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on behalf of the Glyphosate Task Force (GTF)

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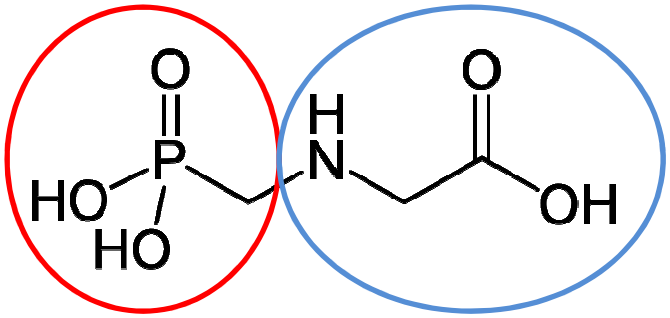
Content

- Genotoxicity
- Carcinogenicity
- Epidemiology
- Embryo-fetal developmental toxicity

Genotoxicity of Glyphosate:
Structural Alerts



- The molecular structure of glyphosate consists of two parts i.e. glycine and methylene phosphonic acid. Both are molecular moeities that don't carry any genotoxic alert or posses oxidative reactivity
- Once absorbed from the gastro-intestinal tract glyphosate is not metabolized and thus does not produce any metabolites that have oxidative reactivity
- Nevertheless, over 80 genotoxicity tests have been performed with glyphosate

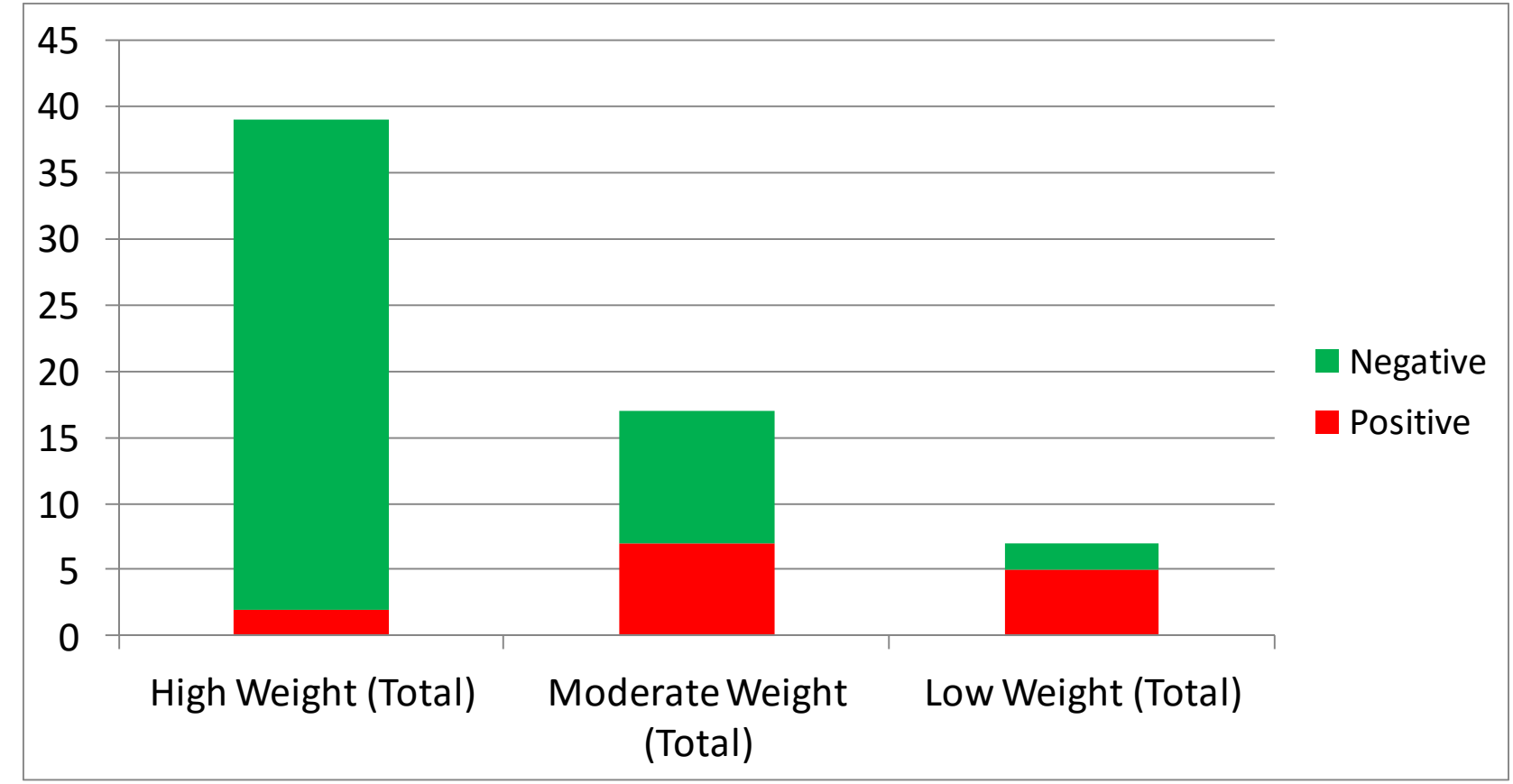
Genotoxicity of Glyphosate:
Weight-of-Evidence Analysis (1)

Endpoint	Negligible Weight		Low Weight		Moderate Weight		High Weight	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
DNA binding (adduct formation) *in vitro*								
DNA binding (adduct formation) *in vivo*			0	1				
SSB/DSB *in vitro* (including comet)			4	0				
SSB/DSB *in vivo* (including comet)					1	0		
SCEs *in vitro*	4	0						
SCEs *in vivo*								
Oxidative DNA *in vitro*								
DNA damage *in vitro*			0	1				
Oxidative DNA *in vivo*					1	1		
DNA damage *in vivo* (8-OHdG adducts)								
DNA repair effects *in vitro*			0	2				
DNA repair effects *in vivo*								
Micronuclei *in vitro*					4	5		
Micronuclei *in vivo*							3	16
Chromosomal aberrations *in vitro*					2	6		
Chromosomal aberrations *in vivo*							0	3
Gene mutation in bacteria (Ames Test)							0	27
Gene mutation mammalian *in vitro*					0	4		
Gene mutation *in vivo*							0	2

Brusick *et al.*, 2016

Genotoxicity of Glyphosate:
Weight-of-Evidence Analysis (2)

Profile of results including GLP studies



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Genotoxicity of Glyphosate:
Conclusion

JMPR is the first international organization that evaluated the genotoxicity of glyphosate using **all** available data (JMPR, 2016) and concluded:

"The overall weight of evidence indicates that administration of glyphosate and its formulation products at doses as high as 2,000 mg/kg bw by the oral route, the route most relevant to human dietary exposure, was **not associated with genotoxic effects** in an overwhelming majority of studies conducted in mammals, a model considered to be appropriate for assessing genotoxic risks to humans"

Genotoxicity of Glyphosate:
Classification

On the basis of the weight-of-evidence analysis of all available data glyphosate should not be classified as a mutagen

Carcinogenicity of Glyphosate:
Long Term Animal Studies

Test species	Studies evaluated*
Mouse	5
Rat	7

*: Only studies that complied with OECD TG and that were conducted according to GLP were considered in this evaluation

- Following carcinogenic responses were evaluated by an independent expert review panel (Williams *et al*., 2016)
  - **In the mouse:**
    - Renal tubular cell adenoma and carcinoma in males
    - Hemangiosarcoma in males
  - **In the rat:**
    - Pancreatic islet-cell adenoma in males
    - Hepatocellular adenoma in males
    - Thyroid C-cell adenoma in males and females

Carcinogenicity of Glyphosate:
Mouse Studies, Expert Panel Conclusions (1)

- **Renal tubule tumors in males (Knezevich and Hogan, 1983):**
  - No dose-response relationship
  - Increase in incidence not statistically significant
  - No dose-response relationship for pre-neoplastic lesions (hyperplasia)
  - No renal tumors in females of the same study despite of higher exposure
  - No confirmation in other mouse studies

Carcinogenicity of Glyphosate:
Mouse Studies, Expert Panel Conclusions (2)

- **Liver hemangiosarcomas in males (Atkinson *et al*., 1993):**
  - No dose-response relationship
  - Increase in incidence not statistically significant (pair-wise comparison)
  - Incidence at the high dose is within the historical control range
  - No increase in the incidence of hemangiosarcoma in females of the same study despite of higher exposure
  - Some mouse studies show no tumors of this type at all at comparable dose levels

Carcinogenicity of Glyphosate:
Rat Studies, Expert Panel Conclusions (1)

- **Pancreatic islet-cell adenoma in males (Stout and Ruecker, 1990):**
  - No dose-response relationship
  - Increase in incidence only statistically significant at low dose
  - Incidence at the low and the high dose slightly above the historical control range of the laboratory
  - No dose-response relationship for pre-neoplastic lesions (hyperplasia)
  - No progression to malignancy
  - No dose-related increase in incidence in females
  - No confirmation in other rat studies

Carcinogenicity of Glyphosate:
Rat Studies, Expert Panel Conclusions (2)

- **Hepatocellular adenomas in males (Brammer, 2001):**
  - Slight dose-response relationship
  - Increase in incidence not statistically significant (pair-wise comparison)
  - Incidence at the high dose at upper limit of the historical control range of the laboratory
  - No progression to malignancy
  - No evidence for pre-neoplastic foci (hyperplasia)
  - No dose-related increase in incidence in other rat studies

Carcinogenicity of Glyphosate:
Rat Studies, Expert Panel Conclusions (3)

- **Thyroid C-cell adenomas in males and females (Stout and Ruecker, 1990):**
  - No dose-response relationship
  - Increase in incidence only statistically significant at mid dose in terminally sacrificed males but not when unscheduled deaths are included
  - Incidence at the high dose still within the historical control range
  - No progression to malignancy
  - No dose-response relationship for pre-neoplastic lesions (hyperplasia)
  - No confirmation in other rat studies

Carcinogenicity of Glyphosate:
Malignant Lymphoma in the male mouse (1)

Study	Incidence (%) of malignant lymphoma										
Dose (mg/kg)	**0**	**15**	**71**	**150**	**165**	**234**	**810**	**838**	**1454**	**4348**	**HC**
Wood *et al.*, 2009	0		2			4	10				0-16
Kumar, 2001[a]	4	10		11					26*		8-24
Kumar, 2001[b]	20	30		32					38*		6-30
Sugimoto, 1997[a]	0				0			0		7	
Sugimoto, 1997[b]	4				4			0		12	4-19

a: terminal kill; b: all animals; * statistically significantly increased when the Z-test is applied at the significance level of 5%.
When the commonly used Fisher's exact test is applied, the statistically significant difference (at the level of 5%) is not confirmed.
Common tumors such as malignant lymphoma in the mouse should be assessed at a statistical significance level of 1%.

Carcinogenicity of Glyphosate:
Malignant Lymphoma in the male mouse (2)

- **Wood *et al*., 2009 study:**
  - No statistically significant increase
  - Incidence in the control group at low end of historical control range
  - All incidences within the historical control range
- **Sugimoto, 1997 study:**
  - No statistically significant increase
  - Incidences (all animals) within the historical control range
  - No dose related increase in pre-neoplastic lesions (plasma cell hyperplasia in cervical lymph nodes)

Carcinogenicity of Glyphosate:
Malignant Lymphoma in the male mouse (3)

- **Kumar, 2001 study:**
  - Statistically significant increase at the high dose only when the Z-test is applied (5% level)
    - The statistically significant difference is not confirmed when the common Fisher's exact test is applied (pair-wise comparison & trend)
    - Statistical significance at the high dose was not adjusted based on common tumors (1% level)
  - Incidence at the high dose slightly beyond the historical control range
  - High dose beyond the limit dose for long term feeding studies (>1000 mg/kg bw/day)
  - Laboratory with a high incidence of spontaneous malignant lymphoma in mice (Swiss albino, HsdOla: MF1)
  - No dose related increase in pre-neoplastic lesions (lymphoid hyperplasia in mesenteric and mandibular lymph nodes)

Carcinogenicity of Glyphosate:
Conclusion Animal Studies

- From the weight-of-evidence analysis of the results from all the mouse and rat studies evaluated, it can be concluded that glyphosate is not a carcinogen in rodents when dosed at levels up to more than 4000 mg/kg bw/day:
  - Lack of statistical significance when appropriate statistics are applied
  - Lack of a clear dose-response relationship
  - Lack of consistency throughout all mouse and rat studies
  - Incidences within (or close to) the historical control range of the laboratory
  - No progression of adenomas to malignancy
  - Increase mostly beyond the limit dose of 1000 mg/kg bw/day
  - Lack of relationship with pre-neoplastic lesions
  - No genotoxicity
  - No plausible mechanism of action including oxidative stress

Carcinogenicity of Glyphosate:
Epidemiology – Assessment of NHL (1)

Validity Factors

Type of bias	Ag health (cohort) study	Case control studies
Recall bias	no	All 6 studies
Selection bias	no	In 4 of 6 studies
Proxy respondents	no	In 3 of 6 studies
Confounding control	extensive	Poor 5 of 6 studies
Sample size	57,311	244 -2348*

*: Number of NHL cases (Acquavella *et al*., 2016)

Carcinogenicity of Glyphosate:
Epidemiology – Assessment of NHL (2)

- Biomonitoring studies in farmers and their families have shown that systemic exposure to glyphosate after application on the field is very low
- Epidemiologic studies have shown that glyphosate is used infrequently
- Recent epidemiology assessments differed based on how the case control studies were interpreted
  - IARC took more of a signal detection approach
  - US EPA considered the Agricultural Health Study (AHS) to be high quality
  - The epidemiology expert panel focused on the AHS cohort study (Acquavella *et al.*, 2016)

Only the AHS study is devoid of major bias issues. The results ("evidence of no association") are consistent with the expectation based on long-term toxicology studies and biomonitoring

Carcinogenicity of Glyphosate:
Classification

On the basis of the weight-of-evidence analysis of all available compliant long term carcinogenicity studies and (unbiased) epidemiology studies, glyphosate should not be classified as a carcinogen

Development Toxicity of Glyphosate:
Overview of Studies

Test species	Studies evaluated*
Rat	6
Rabbit	6

*: Only studies that complied with OECD TG and that were conducted according to GLP were considered in this evaluation

- The rat developmental toxicity studies do not show any evidence of cardiovascular or other types of malformations as a result of glyphosate acid exposure via the oral route at doses of up to 3,500 mg/kg bw/day
- In the rabbit, several test results needed further in-depth evaluation:
  - Maternal toxicity
  - Post-implantation loss
  - Fetal toxicity
  - Cardio-vascular malformations

Development Toxicity of Glyphosate:
Rabbit Studies (1)

- **Maternal toxicity (all studies):**
  - High mortality rate due to mal-gavage, entry of gastric content in the respiratory tract and GI intolerance to glyphosate acid
  - The GI effects (observed in all studies) consisted of soft stools, diarrhea, few to no feces, stasis (hair balls), gastro-enteritis, watery fluid and gas in caecum and rectum which led to a decrease in food consumption and body weight, starvation and abortion

Development Toxicity of Glyphosate:
Rabbit Studies (2)

- **Post-implantation loss (Brooker *et al*., 1991):**
  - Statistically significant increase in post-implantation loss at all dose levels without a dose-effect relationship in one study
  - Late embryonic deaths were also increased but remained within the historical control range whereas there was no dose-effect relationship for early embryonic death
  - The incidence of post-implantation loss in the control group of this study was at the low end of the historical control range
  - This result is not consistent with the outcome of all other 5 rabbit studies where no effect on post-implantation loss was observed

Development Toxicity of Glyphosate:
Rabbit Studies (3)

- **Fetal toxicity (Moxon, 1996):**
  - A statistically significant decrease in mean fetal body weight and a statistically significant increase in skeletal variations was observed in the high dose group in one study
  - These effects are indicative of retardation of fetal development due to the bad health condition of the dams at that dose level (decrease in food consumption, decrease in body weight, GI-effects)

Development Toxicity of Glyphosate:
Rabbit Studies, Cardio-vascular Malformations (1)

Suresh, 1993 study
Number of Fetuses (Litters with Malformations)

Malformations	Dose (mg/kg)			
	0	20	100	500
Number of fetuses examined	133	78	77	28
Seal-shaped heart	1(1)	0(0)	0(0)	0(0)
Cardiomegaly and seal-heart	0(0)	0(0)	1(1)	0(0)
Dilated heart	0(0)	4(3)*	4(2)*	5(2)*
Dilated ventricle (R)	0(0)	0(0)	0(0)	1(1)
Dilated ventricle (L)	0(0)	0(0)	1(1)	0(0)

* Statistically significantly different from control

Development Toxicity of Glyphosate:
Rabbit Studies, Cardio-vascular Malformations (2)

Brooker *et al*., 1991 study
Number of Fetuses (Litters with Malformations)

Malformations	Dose (mg/kg)			
	0	50	150	450
Number of fetuses examined	163	104	112	95
Right sided ascending aorta	0(0)	1(1)	0(0)	0(0)
Narrow/dilated aortic arch/pulmonary trunk/arterial trunk	1(1)	1(1)	1(1)	3(3)
Dorsally displaced pulmonary trunk	1(1)	0(0)	0(0)	0(0)
Retro-esophageal right subclavian artery	0(0)	0(0)	3(1)	2(1)
Single carotid artery	0(0)	1(1)	0(0)	0(0)
Inter-ventricular septal defect	1(1)	1(1)	1(1)	4(4)
Enlarged left, reduced right ventricles	0(0)	0(0)	0(0)	2(2)

Development Toxicity of Glyphosate:
Conclusion Cardio-vascular Malformations

- The increase in the incidence of interventricular septum defect at the high dose was not statistically significant
- Although the incidence (in %, fetal basis) of interventricular septum defect was beyond the historical control range, there was only a **very small difference in absolute terms** i.e. at the high dose the effect was observed in 4 fetuses whereas the maximum number of fetuses with this defect per control group of a comparable size in the historical controls was 3
- The dilated heart (Suresh, 1993) and the ventricular septum defect (Brooker *et al.,* 1991) are not related (different morphogenetic mechanism) and should not be combined in the assessment
- Dilated heart (ill-defined) was not confirmed in the other 5 rabbit studies
- Interventricular septal defect was not confirmed in the other 5 rabbit studies and its incidence was only increased at a dose level with severe maternal toxicity

Developmental Toxicity of Glyphosate: Classification

On the basis of the weight-of-evidence analysis of all available compliant embryo-fetal development toxicity studies, glyphosate should not be classified as toxic to reproduction (embryo-fetal development)

Overall Conclusion

- Based on the weight-of-evidence presented in this assessment, glyphosate **should not** be classified as:
  - a mutagen
  - a carcinogen
  - toxic to reproduction

This is consistent with numerous recent global regulatory agency evaluations

Back-up slides

Genotoxicity of Glyphosate:
Test Results

Test	Result	Comment
Ames	Negative	
In vitro gene mutation tests in mammalian cells	Negative	
In vitro MN	Limited evidence	Absence of induction of CA suggests threshold-mediated aneugenic effects
In vitro and in vivo chromosome aberration	Negative	
In vivo MN	Negative	
In vitro DNA strand breaks	Positive	Probably secondary to toxicity since no chromosome breaks
In vivo DNA strand breaks	Limited evidence of transient DNA strand breakage in vivo	Not associated with DNA adducts
In vitro UDS	Negative	Cultured hepatocytes
In vitro SCE	Positive	The mechanism of induction and the biological relevance of SCE are unclear (negligible weight) and does not contribute to the overall evaluation of genotoxic potential

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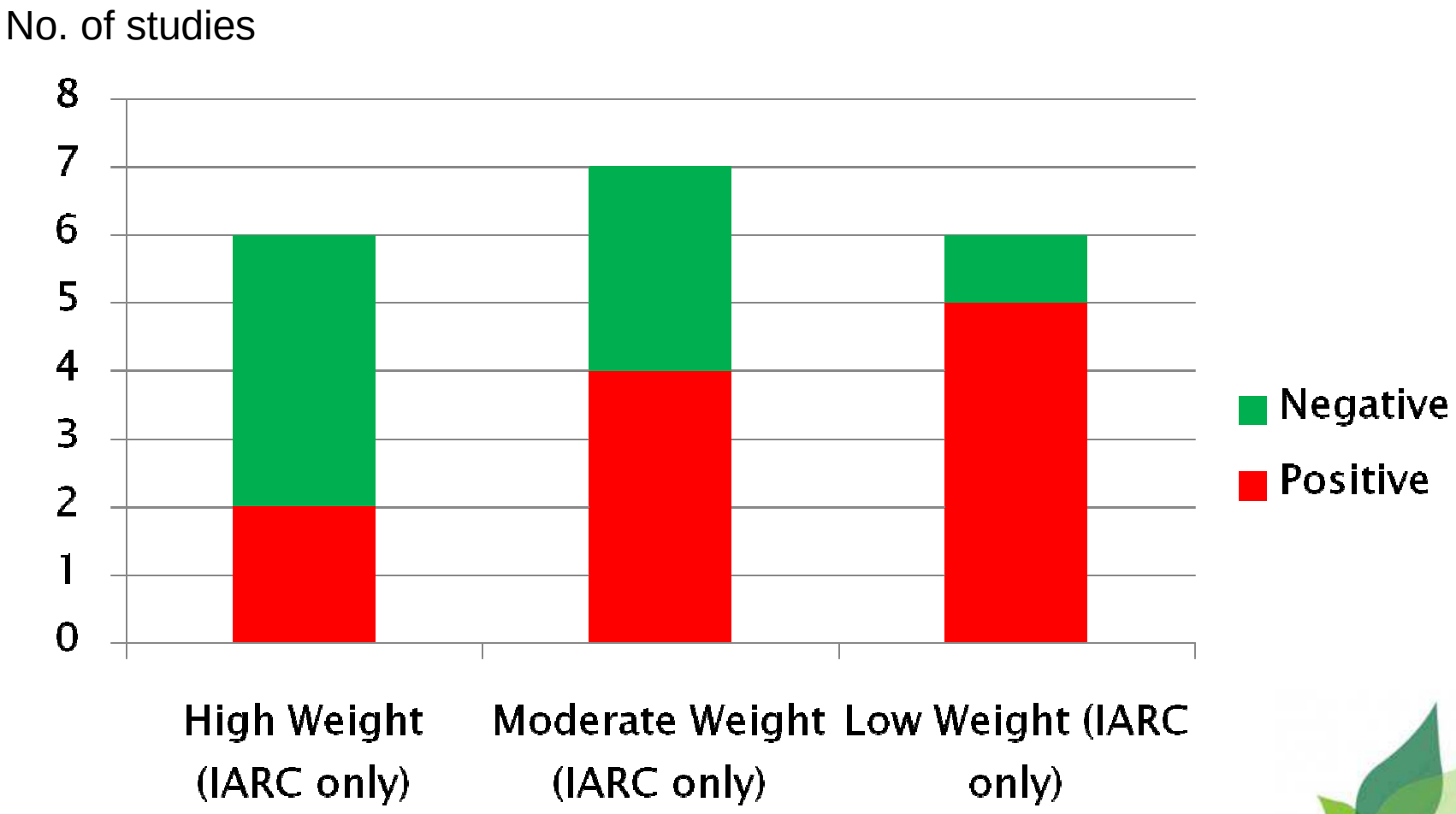
Genotoxicity of Glyphosate:
Weight-of-evidence Analysis by IARC



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Genotoxicity of Glyphosate:
Non-mammalian Studies

- Both major endpoints measured in the majority of non-mammalian tests (i.e. MN and comet) might well produce positive responses that are secondary to toxic effects
- Many of these tests involve exposure by immersion in, or surface contact with, the test material in water
  - This is not a standard or relevant route of exposure for *in vivo* mammalian systems and may introduce route-specific unique toxic and genotoxic effects
  - This is particularly a concern for GBFs which commonly contain surfactants
- **Therefore, we did not consider data from a majority of the non-mammalian systems and non-standard tests with glyphosate, GBF, and AMPA to have significant weight in the overall genotoxicity evaluation, especially given the large number of standard core studies for gene mutations and chromosomal damage available in mammalian systems**

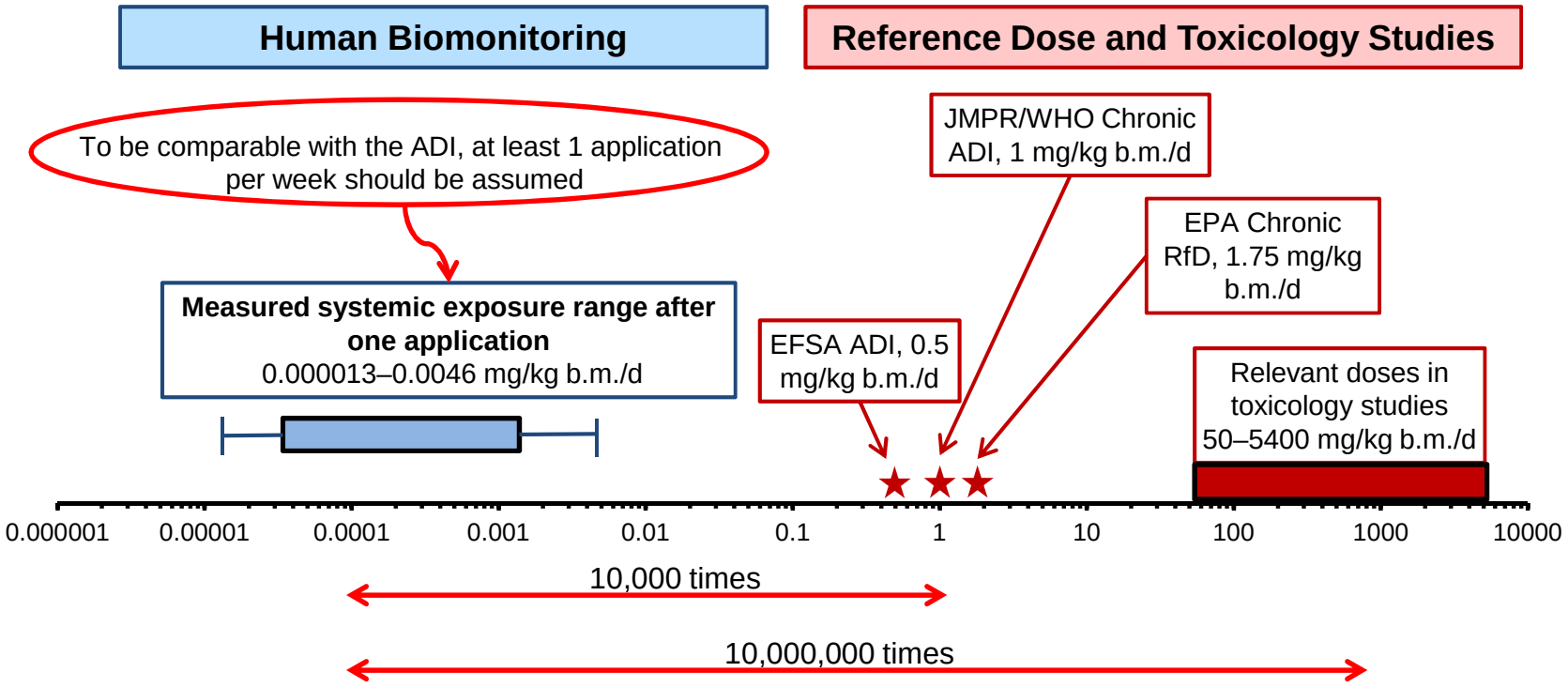
Glyphosate:
Induction of Oxidative stress (1)

- Glyphosate human systemic daily doses (biomonitoring):
  - Max dose: Farmer = 4 µg/kg/day; Spouse = 0.04 µg/kg/day; Children = 0.8 µg/kg/day (Aquavella et al., 2004)
  - Other studies: 0.1-5 µg/kg/day max (reviewed in Bus 2015)
- Animal doses:
  - 2/7 studies: glyphosate at 10 (15 doses) or 300 mg/kg (1 dose) ***ip***
  - 2/7 studies: formulation at 50 or 200 mg/kg (1 dose) ***ip***
  - 1/7 studies: formulation at 50 mg/kg (1 dose) **dermal**
  - 2/7 studies: formulation at 50, 500 mg/kg **gavage** or 0.38% **drinking water**
  - 1/7 studies: mixture of glyphosate (10 mg/kg), zineb (15 mg/kg) and dimethoate (15 mg/kg) ***ip***
- **Test doses 2,500–75,000X higher than maximally exposed farmer**

Glyphosate:
Induction of Oxidative stress (2)

- Glyphosate acid does not contain reactive molecular moeities
- Glyphosate is not metabolized in mammalian species and cannot form oxidative metabolites
- In the majority of studies endpoints were assessed that are only indirect measures of oxidative stress such as depletion of glutathione, production of superoxide dismutase or changes in reactive oxygen species (ROS, H_2O_2)
- **There are no animal studies available where glyphosate acid as such has been administered via a relevant route of exposure (oral) and that led to oxidative damage of DNA**
- Overall, there is no strong weight-of-evidence that glyphosate acid as such produces oxidative damage to DNA in vivo since most of the studies have been conducted with glyphosate-based formulations and/or used irrelevant doses and/or routes of exposure (IP)

Carcinogenicity of Glyphosate:
Epidemiology - Human Exposure



Adapted from: Solomon, 2016

Carcinogenicity of Glyphosate:
NHL Case Control Studies

Study	# NHL cases	# (%) exposed cases	Exposure metric	OR (95% CI)	
McDuffie 2001	517	51(9.9%) 23 (4.4%)	Any use > 2 days/year	1.2 (0.8, 1.7) 2.1 (1.2, 3.7)	✓
Hardell 2002	515	8 (1.6%)	Any use	1.9 (0.6, 6.2)	
De Roos 2003	650	36 (5.5%)	Any use	1.6 (0.9, 2.8)	
Eriksson 2008	910	29 (3.2%) 17 (1.9%)	Any use > 10 days	2.0 (1.1, 3.7) 2.4 (1.0, 5.4)	✓
Orsi 2009	244	12 (4.9%)	Any use	1.0 (0.5, 2.2)	
Cocco 2013	2348	4 (0.2%)	Any use	3.1 (0.6, 17.1)	

Acquavella *et al.,* 2016

Carcinogenicity of Glyphosate:
Ag Health Study & NHL Results

Study	# NHL cases	# (%) exposed cases	Exposure metric	RR (95% CI)
De Roos 2005	92	71 (77)	Any use	1.1 (0.7, 1.9)
	Exposure response analysis	29 (48) 15 (25) 17 (28)	1 to 20 days 21 to 56 days 57 to 2678 days	1.0 0.7 (0.4, 1.4) 0.9 (0.5, 1.6) P_{trend} 0.73

"… the available data provided evidence of no association between glyphosate exposure and NHL incidence." (De Roos *et al.*, 2005)

Analysis of the Results in the Rabbit:
Cardio-vascular malformations

Number of fetuses (litters with malformations)

Study	Dose (mg/kg)													
	0	10	20	50	75	100	150	175	200	300	350	400	450	500
Coles and Doleman (1996)	0(0)			0(0)					1(1)			0(0)		
Moxon (1995)	1(1)					1(1)		0(0)		1(1)				
Hojo (1995)	0(0)	0(0)				1(1)				0(1)				
Suresh (1993)	2(2)		4(3)			6(4)								6(2)
Brooker *et al.* (1991)	1(1)			1(1)			4(3)						5(4)	
Tasker *et al.*, 1980	0(0)				0(0)			0(0)			0(0)			

Analysis of the Results in the Rabbit:
Cardio-vascular malformations (Brooker *et al*., 1991)

Incidence (%, fetal basis)

Malformations	Dose (mg/kg)				Historical control range*
	0	50	150	450	
Number of fetuses examined	163	104	112	95	5964
Narrow/dilated aortic arch/pulmonary trunk/arterial trunk	0.6	1	0.9	3.2	0-1.9** 0-1.7***
Retro-esophageal right subclavian artery	0	0	2.7[a]	2.1[b]	0-1.8
Inter-ventricular septal defect	0.6	1	0.9	4.2[c]	0-2.8
Enlarged left, reduced right ventricles	0	0	0	2.1[d]	0-1

*: 48 vehicle studies performed from January 1989 until October 1993 (Interfauna UK); **: dilated ascending aortic arch; ***: narrow ascending aortic arch; a: 3/112 vs 2/116-152 in the historical controls, and all malformations occurred in one litter; b: 2/95 vs 2/116-152 and all malformations occurred in one litter; c: 4/95 vs 3/106-152 in the historical controls; d: 2/95 vs 1/103-154 in the historical controls.

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