FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR
Bundesinstitut für Risikobewertung

Harmonised Classification and Labelling: Data on Glyphosate for Discussion at RAC-39

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Introduction

- **Germany**
  evaluated data on Glyphosate for two different legal procedures:
- **EU assessment of Glyphosate regarding the renewal of approval according to Regulation (EC) No 1107/2009**
  - Germany is Rapporteur Member State (RMS) and prepared the Renewal Assessment Report (RAR).
  - The **German Federal Institute for Risk Assessment (BfR)** assessed **human health risks** based on **hazard and exposure** assessments.
  - The **German Environment Agency (UBA)** assessed **environmental risks**.
- **EU assessment of Glyphosate regarding the classification and labelling according to Regulation (EC) No 1272/2008**
  - German **Federal Institute for Occupational Safety and Health (BAuA)** is Dossier Submitter (DS) and prepared the dossier to propose harmonized classification and labelling (CLH).
  - The **German Federal Institute for Risk Assessment (BfR)** assessed only **human health hazards,** not considering any human exposure.
  - The **German Environment Agency (UBA)** assessed **environmental hazards**.

Health hazards

- The **toxicological database** for Glyphosate is **exceptionally large** when compared to other pesticides.
- **Full study reports** (toxicology) evaluated by BfR:
  - Re-evaluation of 280 “old” studies (➔ 220 considered as valid)
  - Evaluation of >150 newly submitted studies
- **Open literature publications** (toxicology) evaluated by BfR:
  - Evaluation of >900 studies (ca 220 considered as relevant)

Number of study reports submitted and evaluated for selected endpoints

Toxicological endpoint	Species	studies required	Valid studies submitted
Eye irritation	Rabbit	1	20
(Sub)chronic toxicity	Dog	1	9
Mutagenicity *in vivo*	Mouse/rat	1	18
Carcinogenicity	Rat	1	7
Carcinogenicity	Mouse	1	5
Reproductive toxicity	Rat	1	6
Developmental toxicity	Rat	1	6
Developmental toxicity	Rabbit	1	6

Serious eye damage/eye irritation

- Current entry in Annex VI, CLP Regulation:
  Eye Dam. 1, H318

- Proposal for future entry in Annex VI, CLP Regulation:
  Eye Dam. 1, H318

- Assigned on the basis of irreversible effects on the eye in a number of studies:
  - at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or
  - at least in 2 of 3 animals, a positive response of corneal opacity ≥ 3 and/or iritis > 1.5, calculated as the mean scores following grading at 24, 48, and 72 hours after instillation of the test material.

Specific target organ toxicity – repeated exposure

- Proposal for future entry in Annex VI, CLP Regulation:
  STOT RE 2, H373

- Assigned on the basis of significant toxic effects at generally moderate exposure concentrations in a number of studies:

  - In developmental toxicity studies in rabbits, mortality of does was observed following repeated oral exposure at dose levels ranging from 100 to 500 mg/kg bw per day.

  - It was necessary to use Haber`s rule to adjust the standard guidance values for 28-day and 90-day studies for exposure periods of shorter durations.

Reproductive toxicity – Rat studies

- **No evidence for adverse effects on sexual function and fertility**
  - Based on 6 valid (guideline-compliant) two-generation reproduction toxicity studies in rats.
  - Main effects on the offspring consisted of slightly reduced pup weight or weight gain at high, parentally toxic dose levels.

- **No evidence for adverse effects on development in rats**
  - Based on 6 valid (guideline-compliant) prenatal developmental toxicity studies in rats.
  - Main effects on the offspring consisted of reduced ossification and skeletal anomalies at high, maternally toxic dose levels.

Reproductive toxicity – Rabbit studies

- **No evidence for adverse effects on development in rabbits**
  - Based on 6 valid (guideline-compliant) prenatal developmental toxicity studies in rabbits.
  - Excessive maternal mortality was observed in 2 studies:
    1) at 350 mg/kg bw per day (Tasker et al., 1980) and
    2) at 100 and 500 mg/kg bw per day (Suresh et al., 1993).
  - Maternal deaths observed also in at least 3 further studies.
  - Cardiac malformations (interventricular septal defects) were observed in one study (Brooker et al., 1991) at 450 mg/kg bw per day.
  - These malformations could not be reproduced in 3 newer studies (Hojo, 1995; Moxon, 1996; Coles and Doleman, 1996) using dose levels up to 400 mg/kg bw per day.

Germ cell mutagenicity

- ***In vitro* studies**
  - Bacterial assays: negative
  - Mammalian cell gene mutation assays: negative
  - Chromosomal aberration tests: negative (guideline studies)
  - UDS: negative
  - Induction of SCE and DNA strand breaks: positive

- ***In vivo* studies (in mammals)**
  - Mutagenicity tests (MN or CA in rodent bone marrow);
    - oral administration: negative
    - i.p. administration: negative (guideline studies)
  - Induction of DNA strand breaks: positive
  - Mutagenicity tests in germ cells: negative

- **Weight-of-evidence suggests that Glyphosate does not induce mutations *in vitro* or *in vivo*.**

Carcinogenicity – Rat studies

Study, strain	Liver	Pancreas	Testis	Thyroid
A (1981), SD	No	Yes, but not dose-related	Equivocal	No
B (1990), SD	Equivocal	Yes, but not dose-related	No	Equivocal
C (1993), SD	No	No	No	No
D (1996), Wistar	No	No	No	No
E (1997), SD	No	No	No	No
F (2001), Wistar	No	No	No	No
G (2009), Wistar	No	No	No	No

Carcinogenicity, rat – Conclusion

- **Increased tumour incidences in only 2 out of 7 studies:**
  - Statistically significant (pairwise/low dose) for **pancreatic** islet cell adenomas, (trend test) for **liver** adenomas and **thyroid** C-cell adenomas (Stout & Ruecker, 1990)
  - Statistically significant (pairwise/low dose) for **pancreatic** islet cell adenomas, (trend test & pairwise/"high" dose) for **testicular** interstitial cell tumours (Lankas, 1981).

Additional considerations:

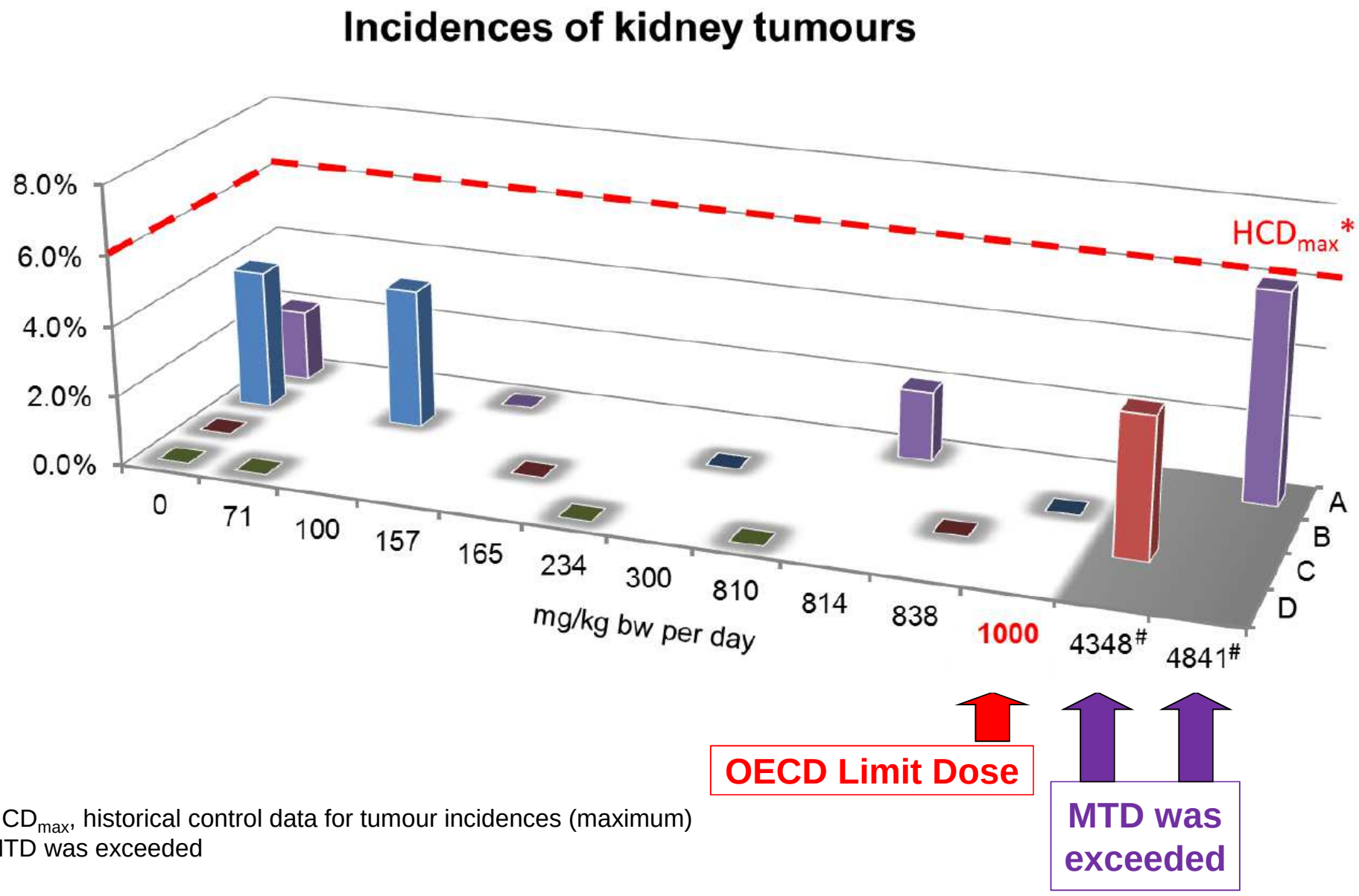
- No monotonic dose response across studies and doses.
- No evidence of supporting pre-neoplastic lesions.
- No evidence of related non-neoplastic lesions.
- No evidence of tumour progression.

- **Weight-of-evidence suggests that tumour findings in rats are not treatment-related.**

Carcinogenicity – Mouse studies

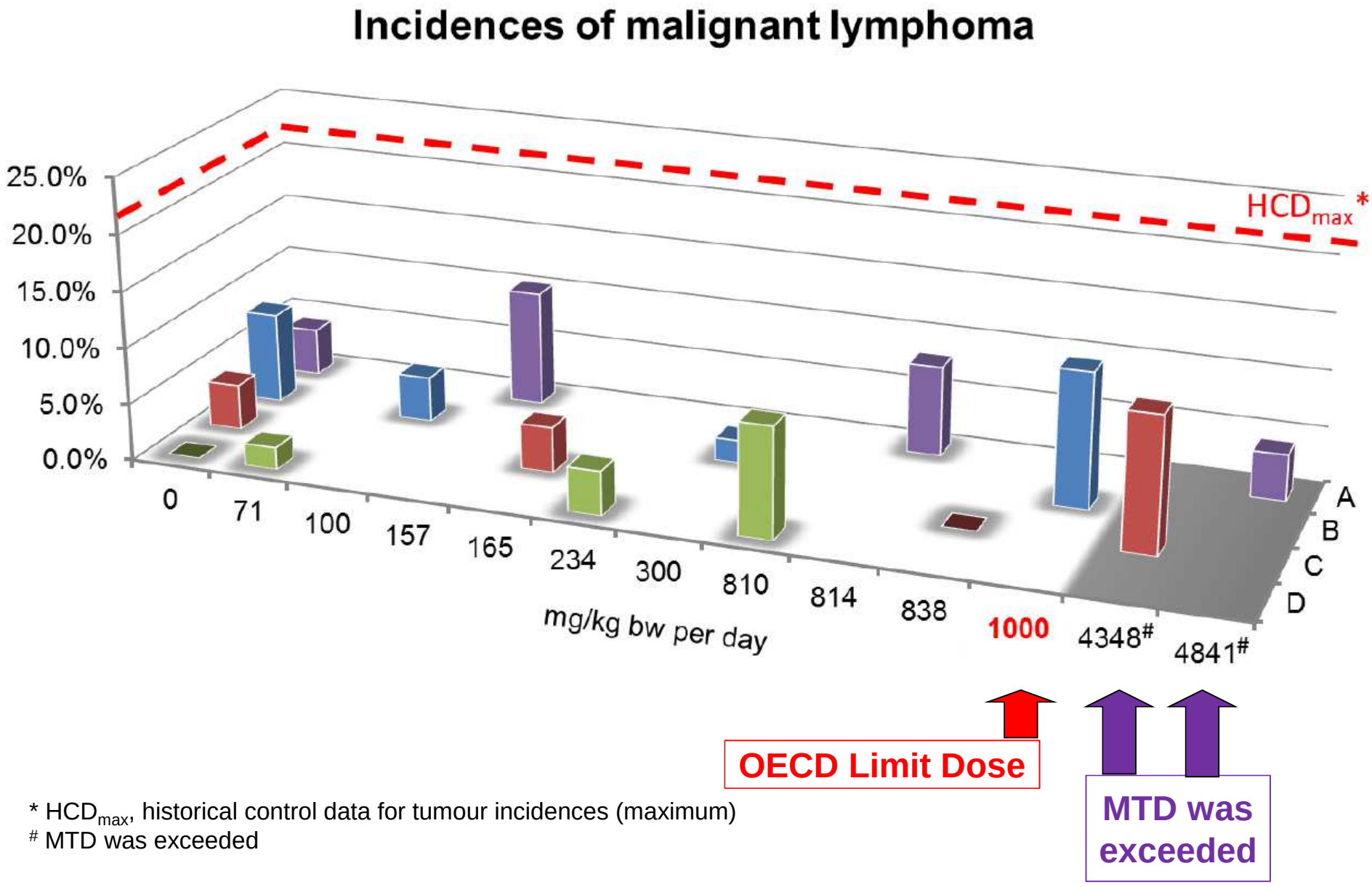
Study, strain	Malignant lymphoma	Kidney tumours	Haemangio-sarcoma
A (1983), CD-1	No	Equivocal	No
B (1993), CD-1	No	No	Equivocal
C (1997), CD-1	Equivocal	Equivocal	Equivocal
D (2001), Swiss	(Equivocal)	Equivocal	No
E (2009), CD-1	Equivocal	No	No

Kidney tumours in male CD-1 mice



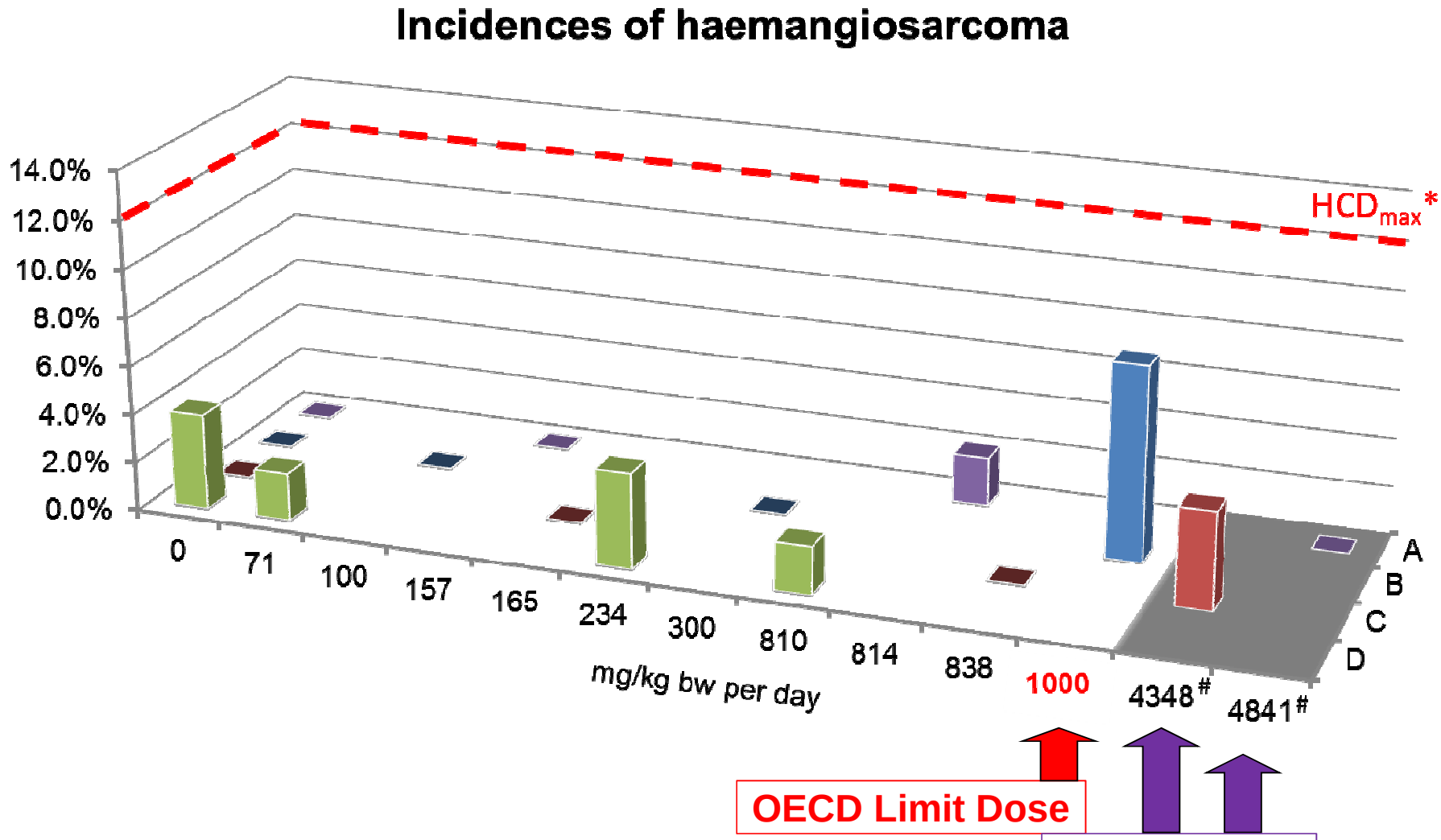
* HCD_{max}, historical control data for tumour incidences (maximum)
# MTD was exceeded

Malignant lymphoma in male CD-1 mice



* HCD_{max}, historical control data for tumour incidences (maximum)
# MTD was exceeded

Haemangiosarcoma in male CD-1 mice



* HCD_{max}, historical control data for tumour incidences (maximum)
\# MTD was exceeded

Carcinogenicity, mouse – Conclusion

- **Higher tumour incidences than in controls in individual studies –** statistically significant in trend test, but never in pairwise comparison

  - **Kidney** tumours in males (Knezevich and Hogan,1983; Sugimoto,1997; Kumar, 2001)
  - **Malignant lymphoma** in males (Sugimoto,1997; Wood et al., 2009)
  - **Haemangiosarcoma** in males (Atkinson et al.,1993; Sugimoto,1997)

  Additional considerations:

  - Low incidences even at excessive doses
  - Incidences within historical control data range
  - No monotonic dose response across studies and doses
  - No evidence of supporting pre-neoplastic lesions

- **Weight-of-evidence suggests that tumour findings in mice are not treatment-related.**

Carcinogenicity – Epidemiological studies

Studies relevant for Glyphosate exposure and NHL

- **Case-control studies**
  - McDuffie et al., 2001: OR 1.26 (0.87-1.8);
    OR 1.20 (0.83-1.74) adjusted effect estimates
  - Hardell et al., 2002: OR 1.85 (0.55-6.2) multivariate, adjusted effect estimates
  - De Roos et al., 2003: OR 2.1 (1.1-4.0) logistic regression
    OR 1.6 (0.9-2.8) hierarchical regression
  - Erikson et al., 2008: OR 2.02 (1.1-3.71) univariate
    OR 1.51 (0.77-2.94) multivariate
  - Orsi et al., 2009: OR 1.0 (0.5-2.2)
- **Cohort studies**
  - De Roos et al., 2005: OR 1.1 (0.7-1.9) adjusted for age, lifestyle factors
- **Meta-analyses**
  - Schinasi/Leon, 2014: OR 1.5 (1.1-2.0)
    OR 1.3 (1.03-1.65) adjusted effect estimates
- **Conclusion: limited evidence for an association between exposure to Glyphosate containing PPP and NHL.**

Carcinogenicity: Weight-of-evidence

- **Weight of evidence approach** should consider that the **toxicological database for Glyphosate** is much **larger than for other pesticides**.
- Conclusions not only based on the **statistical significance** without consideration of the **biological relevance**.
- **Historical control data** provide additional insight into the biological significance of a finding.
- Range of age-related neoplastic and non-neoplastic lesions; consistency of concurrent control tumour incidences should be adequately considered.
- Effects at **excessively high dose** may be of low relevance for evaluating human hazard and human health risk.
- No evidence of **pre-neoplastic lesions** or related non-neoplastic lesions in any target organ in rats and mice.
- No evidence for **progression of lesions** (pre-neoplastic, benign, malignant), or **reduced latency** of neoplastic lesions.

Conclusions - Human health (BfR)

- **in the EU assessment of Glyphosate regarding the renewal of approval according to Regulation (EC) No 1107/2009**
  - **Glyphosate is unlikely to pose a carcinogenic risk to humans**, is unlikely to be genotoxic, and is unlikely to be toxic for reproduction or development.
  - Glyphosate is unlikely to be neurotoxic, immunotoxic or an endocrine disruptor.

- **in the EU assessment of Glyphosate regarding the CLH according to Regulation (EC) No 1272/2008**
  - Harmonized classification and labelling:
    Current entry: **Eye Damage 1** (H318); Aquatic Chronic Toxicity 2 (H411)
    Additional proposal: **STOT RE 2** (H373)
  - **No classification** and labelling is supported for **carcinogenicity**, **mutagenicity** and **reproductive toxicity**.

Conclusions - Human health (Other institutions)

- Institutions which assessed **full study reports of industry studies** and **relevant publications** on Glyphosate:
  - **Australia**: APVMA (2016) – Exposure to glyphosate does not pose a carcinogenic risk to humans
  - **Canada**: PMRA (2015) – Unlikely to pose a human cancer risk
  - **EU**: EFSA (2015) – Unlikely to pose a carcinogenic hazard to humans
  - **Japan**: Food Safety Commission (2016) – No carcinogenicity and genotoxicity
  - **New Zealand**: EPA (2016) – Unlikely to be genotoxic or carcinogenic to humans
  - **WHO**: JMPR (2016) – Unlikely to pose a carcinogenic risk to humans via exposure from the diet

- Institutions which assessed published **study summaries of industry studies** and **relevant publications** on Glyphosate:
  - **WHO**: IARC (2015) – Probably carcinogenic to humans (Group 2A) (limited evidence in humans; sufficient evidence in experimental animals)

Environmental hazards (1)

Legal Entry for Glyphosate (CAS No 1071-83-6)

- In Annex VI CLP-Regulation No 1272/2008 (April 2011):
  - Table 3.1 Aquatic Chronic 2 (H411); GHS09
  - Table 3.2 N, R51-53
  - Hazard Statement: H411: Toxic to aquatic life with long lasting effects
  - based on translation of former classification according to Directive 67/548/EEC to classification according to CLP-Regulation No 1272/2008

Proposal of CLH-Report for Glyphosate

- In CLH-Report (April 2016)
- Hazard Category: Aquatic Chronic 2
- Hazard Statement: H411: Toxic to aquatic life with long lasting effects
  - **based on following data set (lowest effect values):**

– **acute L(E)C_{50} values in concentrations**

- 18 - 22 mg/L for algae *Skeletonema costatum, Anabaena flos-aquae*
- 12 mg/L for aquatic plants *Lemna gibba*
- 84 mg/L for crustaceans (aquatic invertebrates) *Daphnia magna*
- 47 mg/L for fish *Lepomis macrochirus*

– **chronic NOEC values in concentrations**

- 1.82 – 3 mg/L for algae and aquatic plants *Skeletonema costatum, Lemna gibba*
- 12.5 mg/L for crustaceans (aquatic invertebrates) *Daphnia magna*
- 1 mg/L for fish *Brachydanio rerio* according to OECD 212 **(Key study)**

Environmental hazards (2)

Key study for evaluation of long-term aquatic hazard of Glyphosate

Study with *Brachydanio rerio* according OECD 212, (Dias Correa Tavares, 2000)

- semi-static exposure to zebra fish larvae (*Brachydanio rerio*)
- NOEC (168 h) = 1.0 mg/L (nominal)
- valid, robust and reliable study
- lowest reliable long-term toxicity value for glyphosate (from three trophic levels (fish, crustaceans, algae/aquatic plants)
- OECD 212: “It should be borne in mind that only tests incorporating all stages of the life-cycle of fish are generally liable to give an accurate estimate of the chronic toxicity of chemicals to fish, and that reduced exposure with respect to life stages may reduce the sensitivity and thus underestimate the chronic toxicity. It is therefore expected that the embryo and sac-fry test would be less sensitive than the Full Early Life Stage test (OECD 210).”

Glyphosate fulfils classification criteria of long-term aquatic hazard:

- 0.1 mg/L < NOEC ≤ 1.0 mg/L
- Category **Aquatic chronic 2 (H411)** hazardous to the aquatic environment
- “Toxic to aquatic life with long lasting effects“

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Thank you for your attention

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