検索期間：2020年7月～12月

区分ａに分類された文献とその理由

ヒトに対する毒性

1. Information on the study

Data point:	CA 5.8.3
Report author	Ferramosca A. *et al.*
Report year	2021
Report title	Herbicides glyphosate and glufosinate ammonium negatively affect human sperm mitochondria respiration efficiency.
Document No	Reproductive Toxicology (2021), Vol. 99, pp. 48-55
Guidelines followed in study	None
Deviations from current test guideline	Not applicable
GLP/Officially recognised testing facilities	No, not conducted under not conducted under GLP/Officially recognised testing facilities. However, all experiments were performed according to principles of good laboratory practice.
Acceptability/Reliability:	Yes (Relevant, Category A acc. EFSA GD 2092, Point 5.4.1) / Reliable with restrictions

2. Assessment and conclusion

Assessment and conclusion by applicant:

Glyphosate was reported to reduce mitochondrial functionality, by decreasing the oxygen consumption rate in the active and in the passive state of mitochondrial respiration. The mitochondrial respiration efficiency was negatively affected only at concentrations of ≥ 100 nM. In the presence of the sex steroid hormone di-hydroxytestosterone (DHT), the negative effect on mitochondria functionality caused by glyphosate was observed from ≥ 0.1 nM. The passive state of mitochondrial respiration was found to be increased, suggesting a stimulus of mitochondrial respiration independent of ADP phosphorylation. In the presence of the mitochondria-targeting flavonoid quercetin, an increase in oxygen consumption rate was observed at concentrations in the range of 0.1 – 10 nM, reaching the highest levels at glyphosate and quercetin concentrations at 10 nM. Glyphosate was concluded to target mitochondria by using a mechanism that is different from that of DHT and quercetin but not described.

The study did not follow any OECD guideline and was not performed under GLP. No information on the test item with regard to purity was given, however, the supplier and batch number were reported. Cytotoxicity tests were not included, but a broad concentration range from 0.1 - 1000 nM was tested to cover the sexual hormones physiologically relevant concentrations (10 nM), triggering endogenously hormone-dependent signalling pathways, and the estimated (nM range) QRC dietary intake. However, it is not clear how these concentrations may be relevant in term of exposure to glyphosate. The authors stated that these concentration are below the NOAEL and acceptable daily intake (ADI) for the glyphosate (50 and 0.5 mg/kg bw per day, respectively). But no calculations have been presented to show whether spermatozoa could be exposed under the normal condition of glyphosate use. Given the novel study type and underlaying assumptions, evaluation of other comparator molecules to which humans are regularly systemically exposed (e.g. in the diet) would provide context to the relevance of these results and credibility to the assay's predictive capacity for effects in humans.

It was not clear from the publication which solvent has been used for which chemical. As solvent controls were included for all solvents used, the weakness was considered to be of minor degree. The criteria for a biological response were not provided.

Overall, the study is sufficiently documented to generally accepted scientific principles. It is considered to be reliable with restriction, but the information provided are not robust enough to impact the risk assessment.

Reliability criteria for *in vitro* toxicology studies

Publication: Ferramosca, 2021: Herbicides glyphosate and glufosinate ammonium negatively affect human sperm mitochondria respiration efficiency.	**Criteria met? Y/N/Uncertain**	**Comments**
Guideline-specific		
Study is in accordance to valid internationally accepted testing guidelines.	N	
Study is performed according to GLP.	N	
Study is completely described and conducted following scientifically acceptable standards.	Y	
Test substance		
Test material (glyphosate) is sufficiently documented and reported (i.e. purity, source, content, storage conditions)	Y	Purity for glyphosate not reported but batch No. given (#45521, Sigma Aldrich)
Only glyphosate acid or one of its salts is the tested substance.	N	Glyphosate alone and in combination with steroid hormones.
AMPA or other glyphosate metabolites is the tested substance.	N	
Study		
Test system is clearly and completely described.	Y	
Test conditions are clearly and completely described.	Y	
Metabolic activation system is clearly and completely described.	N	
Test concentrations is in physiologically acceptable range (< 1 mM).	Y	0.1-1000 nM
Cytotoxicity tests are reported.	N	Concentration range covers both the sexual hormones physiologically relevant concentrations (10 nM), triggering endogenously hormone-dependent signaling pathways, and the estimated (nM range) QRC dietary intake.
Positive and negative controls.	Y	
Complete reporting of effects observed.	Y	
Statistical methods described.	Y	
Historical negative and positive control data reported.	N	Criteria for a biological relevant response not provided.
Dose-effect relationship reported.	Y	
Overall assessment		
Reliable without restrictions	N	
Reliable with restrictions	Y	No information on the test item with regard to purity was given, however, the supplier and batch number were reported. Cytotoxicity tests were not included, but a broad concentration range from 0.1 - 1000 nM was tested. Historical control data were not reported. Results contradict higher tier in vivo multigenerational studies dosed at several orders of magnitude higher, which do not report any adverse outcomes in fecundity or reproductive outcome. No information on whether the tested concentration may reflect physiological exposure to human spermatozoa in vivo following exposure to the accepted regulatory dose levels following

Publication: Ferramosca, 2021: Herbicides glyphosate and glufosinate ammonium negatively affect human sperm mitochondria respiration efficiency.	**Criteria met? Y/N/Uncertain**	**Comments**
		glyphosate use as herbicide.
Not reliable	N	

1. Information on the study

Data point:	CA 5.9.4
Report author	Shrestha S. *et al.*
Report year	2020
Report title	Pesticide use and incident Parkinson's disease in a cohort of farmers and their spouses.
Document No	Environmental Research (2020), Vol. 191, Article No. 110186 https://doi.org/10.1016/j.envres.2020.110186
Guidelines followed in study	None
Deviations from current test guideline	Not applicable
GLP/Officially recognised testing facilities	Not applicable
Acceptability/Reliability:	Yes (Relevance Category A)/Reliable without restrictions

2. Assessment and conclusion

Assessment and conclusion by applicant:

Glyphosate was not associated with PD in analyses based on ever use or in analyses based on IWLDs of use. Given that there is no plausible mechanism for glyphosate causing PD and that glyphosate systemic dose has been found to be minimal for applicators and spouses (Acquavella et al. 2004), those results are considered to be a valid.

References

Acquavella JF, Alexander BH, Mandel JS, et al. Glyphosate biomonitoring for farmers and their families: Results from the farm family exposure study. Environ. Health Perspect. 2004; 112:321-326.

Reliability criteria for epidemiology studies

Publication: Shrestha S. et al., 2020, Pesticide use and incident Parkinson's disease in a cohort of farmers and their spouses.	**Criteria met? Y/N/?**	**Comments**
Guideline-specific		
Study is in accordance to valid internationally accepted testing guidelines/practices.	n/a	Not applicable
Study is completely described and conducted following scientifically acceptable standards.	Yes	
Test substance		
Exposure to formulations with only glyphosate as a.i.	Yes	
Exposure to formulations with glyphosate combined with other a.i.	No	
Exposure to various formulations of pesticides.	Yes	50 pesticides total
Study		
Study design – epidemiological method followed.	Yes	
Description of population is investigated.	Yes	
Description of exposure circumstances.	Yes	
Description of results.	Yes	
Have confounding factors been considered.	Yes	
Statistical analysis.	Yes	
Overall assessment		

Publication: Shrestha S. et al., 2020, Pesticide use and incident Parkinson's disease in a cohort of farmers and their spouses.	**Criteria met? Y/N/?**	**Comments**
Reliable without restrictions	Yes	The finding of no association between glyphosate and Parkinson's disease risk in this study is considered to be valid. The results fit with what is known about glyphosate toxicology and exposure potential.
Reliable with restrictions	No	
Reliability not assignable	No	
Not reliable	No	

1. Information on the study

Data point:	CA 5.9.4
Report author	Werder E. J. *et al.*
Report year	2020
Report title	Herbicide, fumigant, and fungicide use and breast cancer risk among farmers' wives.
Document No	Environmental Epidemiology (2020), Vol. 4, No. 3, Art. No. e097
Guidelines followed in study	None
Deviations from current test guideline	Not applicable
GLP/Officially recognised testing facilities	Not applicable
Acceptability/Reliability:	Yes (Relevance Category A)/Reliable without restrictions

2. Assessment and conclusion

Assessment and conclusion by applicant:

This study was undertaken based on the assumption that the properties of pesticides – on the endocrine disruption and estrogenic activity scales – are such that an increase in breast cancer risk is possible from direct use of specific pesticides by female AHS spouses or from presumed indirect exposure related to their husbands' use of specific pesticides. The presumed biologic properties of pesticides underlying the study's hypotheses do not apply to glyphosate, at systemic doses from direct or indirect exposure (10^{-4} mg/kg direct, 10^{-5} mg/kg indirect – see Acquavella et al. 2004). The results of the study did not find clear associations between pesticide use and breast cancer risk and results for glyphosate were consistent across the various analyses in indicating no association with breast cancer.

We conclude that this study provides evidence that glyphosate is not related to breast cancer risk.

References

Acquavella JF, Alexander BH, Mandel JS, et al. Glyphosate biomonitoring for farmers and their families: Results from the farm family exposure study. Environ. Health Perspect. 2004; 112:321-326.

Reliability criteria for epidemiology studies

Publication: Werder E. J. et al., 2020, Herbicide, fumigant, and fungicide use and breast cancer risk among farmers' wives.	**Criteria met? Y/N/?**	**Comments**
Guideline-specific		
Study is in accordance to valid internationally accepted testing guidelines/practices.	n/a	Not applicable
Study is completely described and conducted following scientifically acceptable standards.	Yes	
Test substance		
Exposure to formulations with only glyphosate as a.i.	Yes	
Exposure to formulations with glyphosate combined with other a.i.	Uncertain	
Exposure to various formulations of pesticides.	Yes	26 pesticides
Study		

Study design – epidemiological method followed.	Yes	
Description of population is investigated.	Yes	
Description of exposure circumstances.	Uncertain	No description of how farm spouses applied pesticides.
Description of results.	Yes	
Have confounding factors been considered.	Yes	
Statistical analysis.	Yes	Good.
Overall assessment		
Reliable without restrictions	Yes	This study did not show a relationship between glyphosate and breast cancer. That result is consistent with glyphosate's exposure and toxicological properties.
Reliable with restrictions	No	
Reliability not assignable	No	
Not reliable	No	

検索期間：2020年7月～12月

区分ａに分類された文献とその理由

生活環境動植物及び家畜に対する毒性

1. Information on the study

Data point:	CA 8.2.2 and CP 10.2.2
Report author	Du-Carree J.L. *et al.*
Report year	2021
Report title	Impact of chronic exposure of rainbow trout, *Oncorhynchus mykiss*, to low doses of glyphosate or glyphosate-based herbicides.
Document No	Aquatic toxicology (2021), Vol. 230, Art No. 105687
Guidelines followed in study	None
Deviations from current test guideline	Not applicable
GLP/Officially recognised testing facilities	No, not conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes (Relevant, Category A acc. EFSA GD 2092, Point 5.4.1) / Reliable with restrictions

2. Assessment and conclusion

Assessment and conclusion by applicant:

Rainbow trouts were exposed daily to glyphosate (1 µg a.s./L) for 10 month under flow-through conditions. Mortality, reproduction and growth showed no statistical differences between the glyphosate treatment and the control group.

In this study only one concentration was tested (1 µg a.s./L; low-dose). The characteristics and composition of the media used (water) were not fully described. The data on the technical material supports low chronic exposure risk. The test design is such that the fish were too big when used in the study and there is some uncertainty over the influence of the body size on the outcome of the study.

This study has been classified as relevant (Category A acc. EFSA GD 2092, Point 5.4.1) and reliable with restrictions.

1. Information on the study

Data point:	CA 8.2.2 and CA 8.2.2.1 and CP 10.2.2
Report author	Forner-Piquer I. *et al.*
Report year	2021
Report title	Differential impact of dose-range glyphosate on locomotor behavior, neuronal activity, glio-cerebrovascular structures, and transcript regulations in zebrafish larvae.
Document No	Chemosphere (2021), Vol. 267, Art. No. 128986
Guidelines followed in study	OECD TG 236 partially
Deviations from current test guideline	Deviations from OECD TG 236: • Indicators of lethality as coagulation of fertilised eggs, lack of somite formation, lack of detachment of the tail-bud from the yolk sac and lack of heartbeat not reported as recommended in the OECD TG, but growth, cardiac and brain edema, general and brain necrosis, curled tail, pigmentation, tail fin, notochord, eyes, optic capsule and muscles indicators are reported instead. • Validity criteria of overall fertilisation rate, water temperature in test chambers, exposure to positive control and dissolved oxygen at the end of the 96 hrs exposure are not reported. • Apical observations of embryos 24 - 96 hrs post fertilisation are not reported • Water quality (pH, total hardness and conductivity in the control) is not reported • Glyphosate concentration in the lowest test concentration is not reported • Tested concentrations are not spaced by a factor not exceeding 2.2
GLP/Officially recognised testing facilities	No, not conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes (Relevant, Category A acc. EFSA GD 2092, Point 5.4.1) / Reliable with restrictions

2. Assessment and conclusion

Assessment and conclusion by applicant:

Zebrafish (*Danio rerio*) larvae were exposed to glyphosate concentrations between 0.05 and 10.000 µg/L from 1.5 to 120 h post fertilization (hpf). Mortality, cumulative hatching rate and morphological changes showed no significant effects at any glyphosate concentration. Behavioural changes in locomotor were observed at concentrations equal and higher 1000 µg a.s./L. No significant behavioural changes were observed at concentrations lower than 10 µg/L.

A wide range of concentrations (8 between 0.05 and 10.000 µg/L) were tested, which does not allow the estimation of EC_xs. Not all validity criteria according to OECD TG 236 (Fish Embryo Acute Toxicity Test) can be evaluated. Analytical verifications of the test concentrations and some methodological data are not fully reported. In addition, water quality parameters were not reported. The study is partially compliant with the OECD TG 236: Fish Embryo Acute Toxicity Test. Several LOEC and/or NOEC (hatching rate, morphological and behavioural parameters, etc.) can be obtained from the study.

This study has been classified as relevant (Category A acc. EFSA GD 2092, Point 5.4.1) and reliable with restrictions.

1. Information on the study

Data point:	CA 8.3.1.4, CP 10.3.1.5, CP 10.3.1.6
Report author	Odemer R. *et al.*
Report year	2020
Report title	Chronic High Glyphosate Exposure Delays Individual Worker Bee (*Apis mellifera* L.) Development under Field Conditions.
Document No	Insects (2020), Vol. 11, No. 10, Art. No. 664
Guidelines followed in study	OECD TG 75 modified and partially followed in Experiment 1.
Deviations from current test guideline	Deviations to OECD TG 75: • The temperature during the field experiments is only reported as an average of 18.9 °C without knowing if the recommended range of min. 15°C and max. 30°C was kept, to enable a sufficient flight activity of the bees. • Relative humidity and rainfall is not reported for the field experiments. • An assessment of control performance and acceptability of the study has not been stated despite the study appearing to have been conducted according to recognized approaches e.g. OECD 75 semi-field and tunnel test and the Oomen (1992) brood feeding approaches.
GLP/Officially recognised testing facilities	No, not conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes (Relevant, Category A acc. EFSA GD 2092, Point 5.4.1) / Reliable without restrictions

2. Assessment and conclusion

Assessment and conclusion by applicant:

In this study three field and one semi-field tests were conducted in Germany to assess the effect of glyphosate based herbicides (Glyfos Unkraut-Frei® 360 g a.i./L and Roundup® Power Flex 480 g a.i./L) to honey bees (*A. mellifera*). The field studies assessed the effect on the brood and colony development, adult survival, and overwintering success of honey bees, while residues were measured, whereas the semi-field study determined residues of glyphosate based herbicides in different bee relevant matrices.

Glyfos Unkraut-Frei® showed no significant differences in bee survival between the treatments of 4.8 (T1) and 137.6 mg a.i./kg diet (T2) and the control, but hatching weight of adult worker bees was significantly lower (16.7% reduction) and the brood termination (BFD+21) significantly increased when treated with 137.6 mg a.i./kg diet, compared to the control. Roundup® Power Flex did not significantly affect colony development either in summer or during overwintering.

Therefore, the study shows that the tested glyphosate based herbicides did not affect the lifespan of individuals, colony conditions, and overwintering, but delayed worker brood development when applied at a chronic high concentration (137.6 mg a.i./kg diet).

This study has been classified as relevant (Category A acc. EFSA GD 2092, Point 5.4.1) and reliable without restrictions.

検索期間：2020年7月～12月

区分ａに分類された文献とその理由

環境動態

1. Information on the study

Data point:	CA 7.1.4.2
Report author	Albers C. N. *et al.*
Report year	2020
Report title	Leaching of herbicidal residues from gravel surfaces - A lysimeter-based study comparing gravels with agricultural topsoil.
Document No	Environmental pollution (2020), Vol. 266, Art. No. 115225
Guidelines followed in study	None
Deviations from current test guideline	Not applicable
GLP/Officially recognised testing facilities	No, not conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes (Relevant, Category A acc. EFSA GD 2092, Point 5.4.1) / Reliable with restrictions

2. Assessment and conclusion

Assessment and conclusion by applicant:

The article describes mini-lysimeter experiments with glyphosate in agricultural soil as well as in gravel used for construction of gravel paths or driveways. The experiments and results are well described. The LOQ value of 0.13 µg/L for glyphosate is above the current regulatory limit concentration. Glyphosate was not applied as active substance only, but as a product with another strong sorbing active (diflufenican). Therefore, the article is considered reliable with restrictions.

1. Information on the study

Data point:	CA 7.5
Report author	Papagiannaki D. *et al.*
Report year	2020
Report title	Effect of UV-A, UV-B and UV-C irradiation of glyphosate on photolysis and mitigation of aquatic toxicity.
Document No	Scientific Reports (2020), Vol. 10, No. 1, Article No. 20247
Guidelines followed in study	None
Deviations from current test guideline	Not applicable
GLP/Officially recognised testing facilities	No, not conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes (Relevant, Category A acc. EFSA GD 2092, Point 5.4.1) / Reliable with regard to photolysis experiments

2. Assessment and conclusion

Assessment and conclusion by applicant:

The article describes experiments on the effects of UV-A, UV-B and UV-C irradiation on glyphosate photolysis. Experiments on aquatic toxicity were neglected in this evaluation as not found relevant. The photolysis experiments and results are well described. Therefore, the article is considered reliable with regard to the photolysis experiments.

With regards to aquatic toxicity, the publication was considered not relevant.

1. Information on the study

Data point:	CA 7.1.1.2, CA 7.1.3, CA 7.5
Report author	Tauchnitz N. *et al.*
Report year	2020
Report title	Assessment of pesticide inputs into surface waters by agri-cultural and urban sources - A case study in the Querne/Weida catchment, central Germany.
Document No	Environmental pollution (2020), Vol. 267, Art No. 115186
Guidelines followed in study	None
Deviations from current test guideline	Not applicable
GLP/Officially recognised testing facilities	No, not conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes (Relevant, Category A acc. EFSA GD 2092, Point 5.4.1) / Degradation experiments: not reliable Adsorption experiments: not reliable Monitoring data: reliable

2. Assessment and conclusion

Assessment and conclusion by applicant:

The article describes pesticide analyses, amongst them glyphosate, in surface waters and in soil samples within a German catchment area. Additionally, batch adsorption and anaerobic soil degradation experiments were conducted.

For the analyses in surface waters and soil samples, methods and results are well described and conclusive. The respective results are therefore considered reliable.

Maximum concentrations found in composite weekly water samples were 0.90 µg/L for glyphosate and 0.21 µg/L for AMPA. In soil, maximum concentrations comprised of 0.09 mg/kg for glyphosate and 0.17 mg/kg for AMPA.

For the batch adsorption experiment, the methods are well described, however the experimental design is not in agreement with the relevant guideline (OECD 106), e.g. due to use of synthetic rainwater instead of $CaCl_2$ solution, insufficient information on the test concentrations and a temperature of 10 °C. From the information provided, it cannot be concluded on the representativeness of the soils used. Further, besides the final adsorption parameters, no detailed results are reported. Thus, no conclusion can be made on the quality of the results. The adsorption results are therefore considered not reliable.

For the anaerobic degradation experiment, the methods are well described, however the experimental design is not in agreement with the relevant guideline (OECD 307), e.g. due to use of synthetic rainwater, insufficient information on the test concentrations, use of slurry of a liquid-solid ratio of 0.3:1, air-tight incubation and analysis of pore water, only. From the information provided, it cannot be concluded on the representativeness of the soils used. Further, besides the final half-live, no detailed results are reported. Thus, no conclusion can be made on the quality of the results. The results from the anaerobic degradation experiment are therefore considered not reliable.