Title

公表文献調査報告書
グリホサート
別添資料 3
「区分 a」の文献に関する適合性及び信頼性判断理由

ヒトに対する毒性

(Summary of the literature data for Glyphosate: Appendix - Toxicology)

Date

2022-06-27

Author(s)

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目次

Short summary of relevant and reliable articles from category a) with / without restrictions)
Edition No.: M-805380-01-1

Author	Anadon A; Martinez-Larranaga M R; Martinez M A; Castellano V J; Martinez M; Martin M T; Nozal M J; Bernal J L
Source	Toxicology letters, (2009 Oct 08) Vol. 190, No. 1, pp. 91-5. Electronic Publication Date: 14 Jul 2009
Title	Toxicokinetics of glyphosate and its metabolite aminomethyl phosphonic acid in rats .
Publication Year	2009
Accession Number	2009556679
Overall reliability assessment	Reliable with restrictions

Short Summary with assessment and conclusion:
The publication is providing additional information on blood plasma concentrations of glyphosate and AMPA, as well as elimination after oral and i.v. application of glyphosate.
Rats were divided into two groups of 80 animals each, one group (Group 1) received a single oral gavage administration of 400 mg/kg bw glyphosate and the other group (Group 2) received a single i.v. injection of 100 mg/kg bw glyphosate.
Intravenous injection is more rapidly excreted than oral simply because of lag time for gastro intestinal tract absorption and entry into the blood stream. That reported, half-lives for i.v (0.345 and 9.99 hours for α and β phases respectively) versus oral (4.17 and 14.38 hours for α and β phases respectively) are all very rapid elimination kinetics, emphasizing the low duration of any systemic exposure to glyphosate, irrespective of the route.
Study report meets basic scientific principles, and is comparable to actual kinetics guidelines (large number of test animals used, standard deviations and mass balance not reported).

Edition No.: M-812291-01-1

Author	Lindberg Tim; Zeller Kathrin S; Levander Fredrik de Avila Renato Ivan Eriksson Dennis; Chawade Aakash Lindstedt Malin
Source	Journal of proteomics, (2020 Apr 15) Vol. 217, pp. 103647. Electronic Publication Date: 30 Jan 2020 Journal code: 101475056. E-ISSN: 1876-7737. L-ISSN: 1874-3919.
Title	An integrated transcriptomic- and proteomic-based approach to evaluate the human skin sensitization potential of glyphosate and its commercial agrochemical formulations.
Publication Year	2020
Accession Number	2022069835 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
Investigation of molecular mechanisms in the skin sensitization process specifically focusing on DC activation using an integrated transcriptomic- and proteomic approach.
First, Mutz-3-derived cells were exposed to PPD, DMSO, unexposed sample and glyphosate. No cytotoxicity was observed for glyphosate and glyphosate was classified as non-sensitising.
Second, PPD, DMSO, unexposed sample and glyphosate were assembled to protein groups. A clear separation between sensitizers (PPD) and non-sensitizers (unexposed, DMSO, glyphosate) was observed. Data on glyphosate are consistent with other available validated assay results.

The article is classified as reliable with restrictions for the following reason: This is a non-validated test system. The purity and origin of glyphosate is unclear. only 1 dose tested (no dose relationship can be evaluated), no HCD were available in order to compare with the equivalent concurrent controls and test groups results.

Edition No.: M-812260-01-1

Author	Gao Hui; Ding Fan; Chou Xin; Wu Qing Chen Jing; Zhang Xiaoyan Zhang Xiaoyan Zhang Xiaoyan Wan Yi; Hu Jianying
Source	Journal of applied toxicology : JAT, (2019 Mar 25) . Electronic Publication Date: 25 Mar 2019 Journal code: 8109495. E-ISSN: 1099-1263. L-ISSN: 0260-437X.
Title	Activation of the N-methyl-d-aspartate receptor is involved in glyphosate-induced renal proximal tubule cell apoptosis.
Publication Year	2019
Accession Number	2020977263 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

In this study the effect of glyphosate on human proximal tubular epithelial cells was studied in vitro and on mouse kidney in vivo. Tubular epithelial cells (HK-2) in vitro were exposed to glyphosate at concentrations ranging from 20 to 100 μM whereas mice were orally treated with glyphosate at 400 mg/kg bw/day for 28 days. The endpoints investigated for the in vitro study were cell viability, apoptosis, oxidative stress, intracellular Ca2+, expression of the N‐methyl‐D-aspartate (NMDA) receptor and expression of proteins involved in apoptosis. The endpoints explored in the in vivo study in mice were kidney pathology biomarkers, oxidative stress in kidney tissue, kidney histopathology, NMDA receptor immunochemistry and apoptosis in kidney tissue. Glyphosate was found to reduce cell viability, increase the incidence of apoptotic cells with an increase in the expression of apoptosis-related proteins, increase of oxidative stress in a concentration-related manner, increase of the expression of the NMDA receptor and increase Ca2+ influx. Kidney histopathology in mice treated with glyphosate at 400 mg/kg bw/day for 28 days revealed the exfoliation of renal tubular cells. It is postulated by the authors that glyphosate could affect renal tubule epithelial cells via the NMDAR1/[Ca2+]i/ROS pathway. The effects described in this study are not corroborated by regulatory 90–day repeated dose toxicity studies where no renal effects were seen in rats dosed up to more than 4000 mg/kg bw/day and mice dosed up to more than 7000 mg/kg bw/day.

Edition No.: M-813449-01-1

Author	Milic Mirta; Zunec Suzana; Micek Vedran; Kasuba Vilena; Mikolic Anja; Lovakovic Blanka Tariba; Semren Tanja Zivkovic; Pavicic Ivan; Cermak Ana Marija Marjanovic; Pizent Alica; Vrdoljak Ana Lucic; Zeljezic Davor Valencia-Quintana Rafael; Sanchez-Alarcon Ju
Source	Arhiv za higijenu rada i toksikologiju, (2018 Jun 01) Vol. 69, No. 2, pp. 154-168. Journal code: 0373100. E-ISSN: 1848-6312. L-ISSN: 0004-1254.
Title	Oxidative stress, cholinesterase activity, and DNA damage in the liver, whole blood, and plasma of Wistar rats following a 28-day exposure to glyphosate.
Publication Year	2018
Accession Number	2020065563 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

Glyphosate was orally administered to male rats at 0.1, 0.5, 1.75 and 10 mg/kg bw for 28 days to investigate its effect on DNA damage, oxidative stress and cholinesterase activity. The endpoints of this study were DNA damage as measured in the alkaline comet assay, ROS in plasma and liver, lipid peroxidation in plasma and liver, GSH in plasma and liver, GSH-Px activity in whole blood and liver and total cholinesterase, acetyl cholinesterase and butyl cholinesterase activity in plasma. The results of the alkaline comet assays revealed a statistically significant increase in tail length and tail intensity in leucocytes and small and medium sized liver nuclei. With the exception of tail length of small sized liver nuclei no dose-effect relationship was evident. Tail intensity of the leucocytes could not be assessed because of the very high variability of the results. From the results of the oxidative stress markers in plasma and liver and cholinesterase activity in plasma it can be concluded that there was no dose-related effect. In summary, the results do not allow a conclusion on effects of glyphosate on DNA damage, oxidative stress and cholinesterase activity.

Edition No.: M-813432-01-1

Author	Tang Juan; Hu Ping; Li Yansen; Li Chunmei Win-Shwe Tin-Tin
Source	Frontiers in physiology, (2017) Vol. 8, pp. 1083. Electronic Publication Date: 19 Dec 2017 Journal code: 101549006. ISSN: 1664-042X. L-ISSN: 1664-042X. Report No.: PMC-PMC5742203.
Title	Ion Imbalance Is Involved in the Mechanisms of Liver Oxidative Damage in Rats Exposed to Glyphosate.
Publication Year	2017
Accession Number	2019385560 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The objective of this study was to investigate the toxicity, oxidative stress and metal ion concentrations in tissues of rats after oral exposure to glyphosate for 35 days at doses up to 500 mg/kg bw/day. Oxidative stress was studied by the determination of markers of oxidative stress such as SOD, CAT, H2O2, MDA, GSH and GSH-px and the transcription of genes related to inflammation and lipid metabolism. Statistically significant effects were found on body weight, body weight gain, organ weight, serum indicators of liver toxicity and histopathology of the liver and the kidney. Significant changes were also reported on markers of oxidative stress and transcription of genes related to inflammation and lipid metabolism. Many of the effects reported were mild in nature and/or didn't show a clear dose-effect relationship. Also the effects on metal ion concentrations in organ tissues were not always consistent and often didn't show a dose-effect relationship. Moreover, the findings are not corroborated by the regulatory studies of similar test durations and dose ranges.

Edition No.: M-765304-01-1

Author	Mesnage Robin; Biserni Martina; Antoniou Michael N Wozniak Eva; Xenakis Theodoros; Mein Charles A
Source	Toxicology reports, (2018) Vol. 5, pp. 819-826. Electronic Publication Date: 11 Aug 2018 Journal code: 101630272. E-ISSN: 2214-7500. L-ISSN: 2214-7500. Report No.: PMC-PMC6098220.
Title	Comparison of transcriptome responses to glyphosate, isoxaflutole, quizalofop-p-ethyl and mesotrione in the HepaRG cell line.
Publication Year	2018
Accession Number	2020201546 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

Together with three other herbicide active substances (quizalofop-p-ethyl, isoxaflutole and mesotrione) the effect of glyphosate on the transcriptome and metabolome profile of differentiated HepaRG cells was investigated at 0.06, 6 and 600 μM. Glyphosate was found to be only weakly toxic inducing little change in transcriptome profiles when compared with the other herbicides tested. A follow-up metabolomics analysis of HepaRG cells exposed to glyphosate at 0.06 μM revealed a significant decrease in the levels of long chain fatty acids (LCFAs) and polyunsaturated fatty acids (PUFAs). At the higher glyphosate concentrations of 6 and 600 μM, lower lipid levels were also observed but these did not reach statistical significance. It is not clear, however, how these findings from an in vitro tissue culture model can be translated to effects in vivo.N

Edition No.: M-812428-01-1

Author	Kumar Sudhir; Kettleson Eric M; Reponen Tiina; Grinshpun Sergey A Khodoun Marat McKnight Christopher Adhikari Atin
Source	Toxicology, (2014 Nov 05) Vol. 325, pp. 42-51. Electronic Publication Date: 27 Aug 2014 Journal code: 0361055. E-ISSN: 1879-3185. L-ISSN: 0300-483X. Report No.: NLM-NIHMS629285; NLM-PMC4195794; PMC-PMC4195794; MID-NIHMS629285.
Title	Glyphosate-rich air samples induce IL-33, TSLP and generate IL-13 dependent airway inflammation
Publication Year	2014
Accession Number	2015065175 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This study evaluated nose-only exposure to glyphosate and collected farm air samples containing glyphosate and evaluated the immune response in the lungs. This is not a guideline study nor an endpoint used in risk assessment. This study in not usable for risk assessment in terms of hazard assessment. In terms of exposure, the study determined that average amount of glyphosate per filter from environmental samples after spray application to fields was 17.33 µg, which correspond to average airborne concentration of 22.59 ng/m3. The method for the collection and analysis of the air samples was not validated and the assumptions and calculations used in the determination of the average airborne concentration were not provided, therefore the results cannot be verified. While the study itself is acceptable, it is unreliable in terms of usable endpoints for risk assessment.

Edition No.: M-812288-01-1

Author	da Silva Natara D G Carneiro Cristiane E A; Zaia Dimas A M Campos Estefania V R; de Oliveira Jhones L; Fraceto Leonardo F Risso Wagner E Martinez Claudia B R
Source	Toxicology in vitro : an international journal published in association with BIBRA, (2019 Dec 24) pp. 104755. Electronic Publication Date: 24 Dec 2019 Journal code: 8712158. E-ISSN: 1879-3177. L-ISSN: 0887-2333.
Title	Interference of goethite in the effects of glyphosate and Roundup® on ZFL cell line.
Publication Year	2019
Accession Number	2021944846 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
It was shown in this in vitro study that goethite NPs and Roundup® presented cytotoxic and genotoxic effects in ZFL cells and, when co-exposed, produced a synergistic effect. Glyphosate did not promote cytotoxic, biochemical, or genotoxic damage to ZFL cells and, in association, the toxic effects produced by isolated goethite NPs were suppressed by glyphosate. It is concluded therefore that these findings indicate that the presence of other compounds in the formulated product may be responsible for the aquatic organism toxicity of this herbicide when compared to the active ingredient glyphosate.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the test system and glyphosate were not sufficiently characterized and only one concentration of glyphosate was used for testing, preventing any characterisation of dose-response.

Edition No.: M-812485-01-1

Author	Adler-Flindt, Sarah; Martin, Sabine
Source	Toxicology In Vitro, (2019) Vol. 54, pp. 354-366. CODEN: TIVIEQ. ISSN: 0887-2333.
Title	Comparative cytotoxicity of plant protection products and their active ingredients
Publication Year	2019
Accession Number	2018:581036 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

It was the intention of this study to evaluate the GHS classification of pesticide formulations for acute toxicity based on calculated LD50 values using the CLP calculation method (CM). Because of the considerable inaccuracy of this method the in vitro cytotoxicity of 10 pesticide formulations was compared against that of the active ingredient using mouse (3T3) and human (hFF) fibroblasts. In this exercise the IC50 for glyphosate isopropylamine salt was found to be 954.8 ± 117.1 µg/mL for 3T3 cells and 1211 ± 885.7 µg/mL for hFF cells and the IC50 for MON 52276 was 313.2 ± 29.3 µg/mL for 3T3 cells and 361.6 ± 612 µg/mL for hFF cells. The difference in cytotoxicity (expressed as the AUC of the % viability vs concentration curve) between glyphosate and MON 52276 could be regarded as minor.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate isopropylamine salt used was not sufficiently characterized and the standard deviation of the IC50 of glyphosate (1211 ± 885.7 µg/mL) and MON 52276 (361.6 ± 612 µg/mL) for human fibroblasts is too large.

Edition No.: M-769041-01-1

Author	Ilyushina, Nataliya (correspondence); Masaltsev, Gleb; Averianova, Nataliya; Dmitricheva, Olga; Revazova, Yulia; Rakitskii, Valerii Goumenou, Marina Stivaktakis, Polychronis D.; Vardavas, Alexander I.; Tsatsakis, Aristidis M.
Source	Toxicology Reports, (1 Jan 2019) Vol. 6, pp. 105-110. Refs: 22 ISSN: 2214-7500
Title	Maximum tolerated doses and erythropoiesis effects in the mouse bone marrow by 79 pesticides' technical materials assessed with the micronucleus assay.
Publication Year	2019
Accession Number	20180890264 EMBASE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

Along with 51 other pesticides 4 batches of glyphosate with purities ranging from 95.1 to 98.3 % were investigated for their effect on erythropoiesis in mice. To assess the toxicity of glyphosate on the bone marrow the in vivo micronucleus test in the mouse according to OECD test guideline 474 was conducted at the limit dose of 2,000 mg/kg bw. No effect of glyphosate on erythropoiesis was found.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the source of the glyphosate batches used was not reported and no suitable positive control was used in the micronucleus test. The test conducted was in compliance with OECD test guideline 474.

Edition No.: M-812281-01-1

Author	Nagy Karoly Tessema Roba Argaw; Adam Balazs Budnik Lygia Therese
Source	Environmental research, (2019 Dec) Vol. 179, No. Pt B, pp. 108851. Electronic Publication Date: 21 Oct 2019 Journal code: 0147621. E-ISSN: 1096-0953. L-ISSN: 0013-9351.
Title	Comparative cyto- and genotoxicity assessment of glyphosate and glyphosate-based herbicides in human peripheral white blood cells.
Publication Year	2019
Accession Number	2021743619 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This paper describes a well conducted comet assay using human lymphocytes as the test system to examine the genotoxicity and cytotoxicity of glyphosate and 3 commercial products containing glyphosate. No DNA damage was induced by analytical grade glyphosate. The 3 glyphosate products induced an increase in tail intensity in the comet assay only at highly cytotoxic concentrations, non-toxic concentrations induced no DNA damage.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate tested was not sufficiently characterized and no positive control was used.

Edition No.: M-813521-01-1

Author	de Almeida, L. K. S.; Pletschke, B. I.; Frost, C. L.; de Almeida, L. K. S.
Source	3 Biotech (2018), Volume 8, Number 10, 438 p., 84 refs. ISSN: 2190-572X DOI: 10.1007/s13205-018-1464-z Published by: Springer Berlin, Heidelberg URL (Availability): https://link.springer.com/article/10.1007/s13205-018- 1464-z
Title	Moderate levels of glyphosate and its formulations vary in their cytotoxicity and genotoxicity in a whole blood model and in human cell lines with different estrogen receptor status.
Publication Year	2018
Accession Number	2019:277685 CABA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The cytotoxicity of glyphosate has been investigated in whole blood, in hormone independent (MDA-MB-231) and in hormone responsive (MCF7) cell lines and in a an endometrial cancer cell line (HEC1A). The capacity of glyphosate to produce DNA damage was investigated in MCF7, MDA-MB-231 and HEC1A cells in the Comet assay. Glyphosate was found to reduce cell viability in whole blood at the intermediate concentrations (10-250 µg/mL) but not at the highest concentration tested (500 µg/L). A significant concentration related reduction in cell viability was seen with glyphosate in HEC1A cells (> 75 µg/mL) but not in the two other cell lines. When glyphosate was tested at 500 and 1000 µg/mL an increase in tail length and tail moment was observed in HEC1A and MDA-MB-231cells but not in the hormone responsive breast cancer cell line MCF7. The in vitro concentrations of glyphosate at which DNA damage was observed were 500 and 1,000 µg/mL which are systemic concentrations that cannot be reached in in vivo toxicology studies. This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the Comet assay was only conducted at concentrations that are physiologically not feasible in in vivo toxicology studies (> 1mM).

Edition No.: M-813456-01-1

Author	Santovito Alfredo; Ruberto Stefano; Gendusa Claudio; Cervella Piero
Source	Environmental science and pollution research international, (2018 Dec) Vol. 25, No. 34, pp. 34693-34700. Electronic Publication Date: 15 Oct 2018 Journal code: 9441769. E-ISSN: 1614-7499. L-ISSN: 0944-1344.
Title	In vitro evaluation of genomic damage induced by glyphosate on human lymphocytes.
Publication Year	2018
Accession Number	2020396638 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
This paper describes human lymphocyte chromosome aberration and micronucleus tests with glyphosate. Although broadly compliant with OECD 473 and 487 there are some critical deficiencies which will have adversely influenced the reliability of the findings. Treatment with glyphosate was initiated 24 hours after lymphocyte cultures were stimulated to divide, instead of the recommended 48 hours, consequently the cultures would not have been asynchronous. This could mean cells in some stages of the cell cycle may have been under-represented, whilst others over-represented. Exposure to glyphosate was continuous for 28 hours in the chromosome aberration assay or 48 hours in the micronucleus assay. In contrast OECD test guidelines recommend maximum exposure of 1.5 cell cycles, equivalent to approximately 24 hours for lymphocyte cultures. For both endpoints the paper does not confirm if the slides were coded prior to analysis. The positive control has been compared statistically to the glyphosate treated cultures rather than the solvent controls.
The authors consider that glyphosate induces tri-tetraradial aberrations (amongst other aberration types) but fails to comment that the frequency of these aberrations observed at a single glyphosate concentration is 3-fold lower than the frequency observed in the solvent control cultures. Furthermore, it is unusual that the only multi-aberrant metaphases observed were a small number of positive control metaphases and gaps did not appear to increase with treatment but chromatid and chromosome breaks did.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate tested was not sufficiently characterized and although the genotoxicity tests conducted were in general in accordance with the OECD test guidelines, significant deficiencies were noted.

Edition No.: M-813307-01-1

Author	Kasuba Vilena; Milic Mirta; Rozgaj Ruzica; Kopjar Nevenka; Mladinic Marin; Zeljezic Davor Mladinic Marin Zunec Suzana; Vrdoljak Ana Lucic Pavicic Ivan; Cermak Ana Marija Marjanovic Pizent Alica; Lovakovic Blanka Tariba
Source	Environmental science and pollution research international, (2017 Aug) Vol. 24, No. 23, pp. 19267-19281. Electronic Publication Date: 30 Jun 2017 Journal code: 9441769. E-ISSN: 1614-7499. L-ISSN: 0944-1344.
Title	Effects of low doses of glyphosate on DNA damage, cell proliferation and oxidative stress in the HepG2 cell line.
Publication Year	2017
Accession Number	2018735648 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The objective of this study was to examine the effects of acute exposure (4 and 24 hours) of human hepatoma HepG2 cells to glyphosate at concentrations equivalent to the systemic concentrations at the ADI, REL and OEL. The endpoints investigated in this study are cell proliferation, DNA damage, MN formation and oxidative stress. A non-statistically significant increase in cell proliferation was seen in the CCK-8 test with no dose-effect relationship. The comet assay showed a statistically significant decrease in tail intensity after 4 hours with no difference from control after 24 hours. In the CBMN cytome assay a non-statistically significant increase in BN MN frequency was seen after 4 hours without a dose-effect relationship. After 24 hours, a decrease instead of an increase in BN MN frequency was reported. The nuclear bud frequency was statistically significantly elevated after 4 hours of exposure but was statistically significantly lower than control after 24 hours of exposure. The indicator tests for oxidative stress did not show a substance related effect.

Overall, the results of the study do not indicate a genotoxic potential of glyphosate. The lack of statistical significance, reproducible effects as well as the fact that the control values in the Comet assay and micronucleus assay seem to be highly variable limit the reliability of the study.

This publication is considered relevant but reliable with restrictions because the cytogenetic damage found in vitro at a systemic concentration corresponding with the ADI (0.5 µg/mL which should have been 0.17 µg/mL) was not confirmed in in vivo regulatory MN studies with doses up to 2000 mg/kg bw corresponding with a systemic concentration of about 50 µg/mL.

Edition No.: M-813282-01-1

Author	Kwiatkowska, Marta; BoA14ena Bukowska; Edyta Reszka; Ewa JabAX82oAX84ska; Jaromir MichaAX82owicz; Katarzyna WoAniak
Source	Food and chemical toxicology (2017) ISSN: 0278-6915 Published by: Elsevier Ltd Source Note: 2017,
Title	DNA damage and methylation induced by glyphosate in peripheral blood mononuclear cells (in vitro study)
Publication Year	2017
Accession Number	2017:292067 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

It was the objective of this study to investigate the effect of high glyphosate concentrations on DNA integrity and DNA methylation in PBMCs in vitro. It was demonstrated that glyphosate increased statistically significantly DNA damage (single and double strand-breaks and alkali-labile sites formation) from 0.5 mM up to 10 mM. Repair of the DNA lesions was significant at all concentrations tested after 120 minutes of recovery. The percentage of the global DNA methylation level was statistically significantly decreased by glyphosate at 0.25 mM but not at 0.5 mM. On the contrary, p53 promoter region methylation was statistically significantly increased as compared to control cells at 0.25 and 0.5 mM.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the lowest concentration at which DNA damage was observed (0.5 mM) is higher than the blood concentrations in rats (0.3 mM) obtained after dosing at the limit dose of 2000 mg/kg bw where no MN effects were seen.

Edition No.: M-813279-01-1

Author	Suarez-Larios, Karen ; Salazar-Martinez, Ana-Maria ; Montero-Montoya, Regina
Source	Journal of Toxicology, 20170101 ISSN: 1687-8191; 1687-8191 E-ISSN: 1687-8205; 1687-8205 DOI: 10.1155/2017/3574840 Published by: Hindawi Limited, New York
Title	Screening of Pesticides with the Potential of Inducing DSB and Successive Recombinational Repair
Publication Year	2017
Accession Number	2017:233331 PQSCITECH
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The objective of this study was to assess whether glyphosate and its metabolite AMPA produced DNA double strand breaks in human peripheral lymphocytes and whether proteins involved in DNA repair were induced. The results show that glyphosate, but not AMPA, increased the mean of the percent cells with more than 10 γ-H2AX foci, however, without a clear dose-effect relationship. Glyphosate was found to induce statistically significantly a protein involved in DNA repair, p-Ku80, at 5 µM without a dose-effect relationship (when measured as median OD).

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because glyphosate as a test chemical was not sufficiently characterized and the effect found on an indicator of DNA double strand breaks was not concentration related and occurred at concentrations that were much lower than the systemic concentrations (approx. 300 µM) of regulatory in vivo MN tests at 2000 mg/kg bw which were negative.

Edition No.: M-812479-01-1

Author	Townsend Michelle; Peck Connor; Meng Wei; Robison Richard Heaton Matthew O'Neill Kim
Source	Regulatory toxicology and pharmacology : RTP, (2017 Apr) Vol. 85, pp. 79-85. Electronic Publication Date: 6 Feb 2017 Journal code: 8214983. E-ISSN: 1096-0295. L-ISSN: 0273-2300.
Title	Evaluation of various glyphosate concentrations on DNA damage in human Raji cells and its impact on cytotoxicity.
Publication Year	2017
Accession Number	2018255653 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

The purpose of this study was to investigate the concentration and time dependent DNA damaging potential of glyphosate in Burkitt's B Cell Lymphoma (Raji) cells using the comet assay and MTT viability assay. The cells were exposed to glyphosate concentrations ranging from 0.1 µM to 15 mM and resulting DNA damage and loss of cell viability were measured after various lengths of exposure. DNA damage could only be observed at 1mM and higher which are concentrations that cannot be attained in vivo. The DNA damage seen at 1 and 5 mM reached its maximum between 60 and 80 minutes of incubation which returned to control values thereafter. To reach 1 mM of systemic concentration in vivo experimental animals have to be treated orally with glyphosate at dose levels that are much higher than those used in long term carcinogenicity studies which showed no carcinogenic effect of glyphosate.

This publication is considered relevant for the risk assessment of glyphosate and reliable without restrictions because it complies with most of the reliability criteria for in vitro testing although no historical control data were reported. The significance for the risk assessment of glyphosate is limited because DNA damage has only been demonstrated at concentrations of glyphosate that cannot be attained in in vivo test systems.

Edition No.: M-812416-01-1

Author	Roustan A; Aye M; De Meo M; Di Giorgio C
Source	Chemosphere, (2014 Aug) Vol. 108, pp. 93-100. Electronic Publication Date: 12 Apr 2014 Journal code: 0320657. E-ISSN: 1879-1298. L-ISSN: 0045-6535.
Title	Genotoxicity of mixtures of glyphosate and atrazine and their environmental transformation products before and after photoactivation
Publication Year	2014
Accession Number	2014773701 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The cytogenetic effect of two herbicides (glyphosate and atrazine), their metabolites (AMPA and DEA), and mixtures thereof was investigated in CHO-K1 cells in the in vitro micronucleus test. Only the results of glyphosate and AMPA tested alone are reported and discussed in the summary. Glyphosate and AMPA were tested with and without metabolic activation and with light irradiation. Also the potency of glyphosate and AMPA to produce ROS was investigated. The concentrations tested ranged from 5 to 100 µg/mL for glyphosate and from 0.00005 to 5 µg/mL for AMPA. No statistically significant increase in the incidence of bi-micronucleated cells (BMC) was observed with glyphosate at concentrations up to 100 µg/mL in the dark and without metabolic activation. However, a statistically significant and dose-related increase in BMC was noted from 10 µg/mL in the presence of metabolic activation. With light irradiation a statistically significant increase in BMC was noted for glyphosate at a concentration of 100 µg/mL. AMPA produced a statistically significant and dose-related increase in BMC from a concentration of 0.01 µg/mL in the dark and without metabolic activation. With metabolic activation a statistically significant increase in BMC was seen with AMPA from 1 µg/mL. With light irradiation the lowest test concentration of AMPA with a statistically significant increase in BMC was 0.0005 µg/mL. Only AMPA was found to produce an elevated oxidative effect, whereas the oxidative potency of glyphosate was very low. The results of glyphosate in the in vitro micronucleus test with metabolic activation reported in this study are surprising since glyphosate is essentially unmetabolized in vitro in the presence of a rat liver S9 homogenate. Moreover, these results are not corroborated by regulatory in vivo micronucleus tests in the mouse dosed up to more than 2,000 mg/kg bw.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate and AMPA tested were not sufficiently characterized and no positive and control historical data were reported. The in vitro micronucleus test carried out was in compliance with OECD TG 487.

Edition No.: M-813192-01-1

Author	Manas, F.; Peralta, L.; Garcia Ovando, H. Ugnia, L.; Weyers, A.; Gorla, N. Gorla, N.
Source	BAG - Journal of Basic and Applied Genetics, (December 2013) Vol. 24, No. 2, pp. 67-75. Refs: 43 ISSN: 1666-0390 CODEN: BAGABA
Title	Oxidative stress and comet assay in tissues of mice administered glyphosate and ampa in drinking water for 14 days.
Publication Year	2013
Accession Number	2014120985 EMBASE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The objective of this study was to investigate the effect of glyphosate and AMPA on indicators of oxidative stress and DNA integrity in mice after oral exposure for 14 days via the drinking water. The results of this study indicate that no statistically significant differences have been found in liver, kidney, lung and heart for all oxidative stress parameters measured with the exception of a decrease in SOD activity in the heart and an increase in CAT activity in the kidney at a daily glyphosate dose of 400 mg/kg bw. There was an increase in CAT activity in the lung but this was not statistically significant and did not show a dose-effect relationship. A statistically significant increase in DNA damage parameters was observed for glyphosate and AMPA with the exception of tail intensity in the liver for glyphosate at 40 mg/kg bw/day. No clear dose-effect relationship was evident for DNA damage parameters in blood after treatment with glyphosate. A dose-effect relationship was present for tail length and tail moment in the liver.

This publication is considered relevant for glyphosate risk assessment but reliable with restrictions because the increased DNA damage seen (only 2 dose levels tested for glyphosate with too few animals) didn't show a dose-effect relationship in blood and occurred at dose levels (40 and 400 mg/kg bw/day) that are much lower than the 2000 mg/kg bw used in regulatory in vivo MN tests in the mouse with negative results.

Edition No.: M-812361-01-1

Author	Koller Verena J Furhacker Maria; Nersesyan Armen; Misik Miroslav; Eisenbauer Maria; Knasmueller Siegfried
Source	Archives of toxicology, (2012 May) Vol. 86, No. 5, pp. 805-13. Electronic Publication Date: 14 Feb 2012 Journal code: 0417615. E-ISSN: 1432-0738. L-ISSN: 0340-5761.
Title	Cytotoxic and DNA-damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells.
Publication Year	2012
Accession Number	2012429255 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

The objective of the present study was to find out whether exposure of human-derived buccal epithelial TR146 cells to glyphosate and Roundup causes adverse effects. In cytotoxicity experiments, four different endpoints were used, which reflect different modes of action. To assess the effect of glyphosate and Roundup on DNA stability, single cell gel electrophoresis assays (SCGE) were conducted under standard alkaline conditions reflecting the formation of single- and double-strand breaks. Additionally cytokinesis-block MN cytome assays have been conducted in which different nuclear anomalies were measured. This study demonstrated that there is a big difference in cytotoxicity between glyphosate and Roundup. This is not surprising since the surfactants present in glyphosate formulations decrease the integrity of cell and mitochondrial membranes causing toxicity and ensuing DNA instability. Glyphosate was found to significantly increase tail intensity as of 20 mg/L but without any further increase with dose from 40 to 2000 mg/L. Roundup increased in a dose dependent manner the tail intensity from 20 mg glyphosate eq./L up to 200 mg glyphosate eq./L with increasing cytotoxicity and 0 % cell integrity at 200 glyphosate eq. mg/L. This indicates that there is a relationship between the cytoxicity of Roundup and DNA instability. This study has demonstrated a greater sensitivity of buccal epithelial cells for glyphosate and its formulations than hematopoietic cells where no effects have been noted in in vivo MN tests with doses up to 2,000 mg/kg bw. Since there is no direct exposure of the buccal epithelium with the Roundup formulation (unless it is swallowed) during application and the inhalation of aerosol of the spray dilution during application is negligible (Jauhiainen A et al. (1991) Am. Ind. Hyg. Assoc. J. 52, 61–64) the likelihood of DNA damage in epithelial cells of the GI and the respiratory tract remains very low.

This publication is considered relevant for the risk assessment of glyphosate and reliable with restrictions. Although it complies with most of the reliability criteria of an in vitro toxicology study, no blinded scoring of coded slides is reported. Also, concentrations with positive findings (20-2000 mg/L) noted significant effects on necrosis and apoptosis markers in parallel experiments at the low dose of 20 mg/mL.

Edition No.: M-812295-01-1

Author	Crump Kenny Crouch Edmund Zelterman Daniel Crump Casey Haseman Joseph
Source	Toxicological sciences : an official journal of the Society of Toxicology, (2020 Jun 01) Vol. 175, No. 2, pp. 156-167. Journal code: 9805461. E-ISSN: 1096-0929. L-ISSN: 1096-0929.
Title	Accounting for Multiple Comparisons in Statistical Analysis of the Extensive Bioassay Data on Glyphosate.
Publication Year	2020
Accession Number	2022253558 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

Ten cancer bioassays of sufficient quality and which allowed the analysis of individual animal data was selected for the application of a multi-response permutation procedure that adjusts for the large number of tumors eligible for statistical testing and provides valid false-positive probabilities. The statistical tests applied in the analysis were functions of p-values obtained from conventional continuity-corrected poly-3 tests for trend applied to each type of tumor or combination of tumor types in each bioassay. Results from 3 multi-response permutation tests are reported and discussed: the “min-test”, the “05-test” and the “01-test”. In the min-test, the test statistic is the smallest p-value obtained from applying the poly-3 test to all tumor types in all bioassays investigated. Animals are randomly reassigned to dose groups in a Monte Carlo analysis, keeping the total numbers of animals in each dose group equal to the number in the original data. The tumors in each such reassignment are analyzed using the poly-3 test in exactly the same way as in the original data. Males and females are permuted separately. The false positive rate is the proportion of random reassignments that result in a smallest poly-3 p-value that is smaller than or equal to the smallest poly-3 p-value obtained from the original data. The test statistics for the 05-test and the 01-test are the number of poly-3 tests of tumors in the original data for which the p-value is less than or equal to the critical value of 0.05 or 0.01, respectively. In all applications of the poly-3 test, the test is applied only to data from one sex in a single study and the p-values from the poly-3 tests of all the studies are combined to create the “global” tests (min-test, 05-test and 01-test) to give the correct false positive rates. In addition to the randomization procedures for testing for positive dose-response trends in tumor incidence, the same procedures were repeated after reconfiguring the poly-3 test for negative trends. When the frequency of poly-3 p-values for positive trend computed from all tumors in all 10 bioassays in which at least two tumors occurred are considered there is an excess of large p-values (close to 1.0) compared to small p-values (close to 0.0). Since the version of the poly-3 trend test applied is a one-sided test for a positive trend, p-values close to 1.0 would translate into p-values near 0.0 for one-sided trend tests for anti-carcinogenicity. Results of tests for a dose-related decrease in survival in each study show that in none of the bioassays analyzed this test was statistically significant. Moreover, 4 of the datasets had p-values in excess of 0.95 which indicates a significant positive trend in survival with increasing dose. The most significant poly-3 trend in all 10 bioassays was found in the Atkinson et al. (1993) study for hemangiosarcoma in male mice with a p-value of 0.0013. The actual significance of this smallest p-value, which is the false positive rate for the min-test,

was 0.26 based on the primary analysis, rather than the naive value of 0.0013. This means that 26 % of the randomizations of the 10 datasets gave a smallest p-value less than or equal to the smallest p-value obtained from the original data. Besides, the incidence in hemangiosarcomas (8 %) remained within the historical control range and no such tumors were identified in another mouse study at a dose level nearly 5 times of that used in the Atkinson et al. (1993) study. Overall, these findings suggest that, after accounting for the number of statistical tests performed, there was no clear evidence of a positive dose-related trend in tumor occurrence. The 01-test for a negative trend was highly significant with a p-value of 0.002. These findings suggest stronger evidence for negative rather than positive dose-response trends in tumor occurrence. In all 10 bioassays investigated, the analysis made in this paper identified 24 tumors that exhibited a poly-3 positive trend with a p-value of less than or equal to 0.05. Nevertheless, after accounting for the multitude of statistical tests this analysis did not find that number statistically significant ($p = 0.08$). The statistical analysis of 10 glyphosate bioassays presented in this paper found no strong statistical evidence that glyphosate is carcinogenic. This publication is considered relevant for the risk assessment of glyphosate and reliable without restrictions because state-of-the-art statistical methods were employed to a selected set of cancer bioassays to demonstrate false-positive probabilities.

Edition No.: M-813485-01-1

Author	Portier Christopher J
Source	Environmental health : a global access science source, (2020 Feb 12) Vol. 19, No. 1, pp. 18. Electronic Publication Date: 12 Feb 2020 Journal code: 101147645. E-ISSN: 1476-069X. L-ISSN: 1476-069X. Report No.: PMC-PMC7014589.
Title	A comprehensive analysis of the animal carcinogenicity data for glyphosate from chronic exposure rodent carcinogenicity studies.
Publication Year	2020
Accession Number	2022114018 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

Thirteen glyphosate cancer bioassays considered acceptable for this re-analysis were selected from the published literature, the EPA review, the review from the German Institute for Risk Analysis, the JMPR review, and full laboratory reports. For twelve of them full study reports were available. Individual tumour counts for the individual studies were re-analyzed using the exact Cochran-Armitage one-sided linear trend test. Re-analyses were conducted on all primary tumours where there were at least 3 tumours in all of the animals in a sex/species/strain combination. In addition, any tumour where a significant positive trend ($p \leq 0.05$) was found in at least one study was also evaluated in all the other studies of the same sex/species/strain combination, regardless of the number of animals with the tumour. Pairwise comparisons between individual exposed groups and the control group were conducted using Fisher's exact test. To evaluate the consistency of a tumour finding across multiple studies using the same sex-species-strain combinations, logistic regression with individual background responses and dose trends are fit to the pooled data using maximum likelihood estimation. The same methods of analysis were used to evaluate the incidence of non-neoplastic lesions in tissues where tumours were observed. In cases of rare tumours where the increase in incidence didn't reach statistical significance the test proposed by Tarone (1982) was applied using an appropriate historical control group. To summarize the results of the strength-of-evidence analysis, each tumour is placed in any of the following categories: Clear evidence (CE), some evidence (SE), equivocal evidence (EE), and no evidence (NE). The factors used to place tumours into these categories include the analyses of the individual studies, the consistency of the data across studies (pooled analyses), the analyses using historical control data, the analyses of non-neoplastic lesions, and mechanistic evidence with the associated scientific literature. The author's weight-of-evidence analysis indicates that there is clear evidence (CE) that oral exposure to glyphosate *via* the diet produces adrenal cortical carcinoma in the female SD rat, hemangioma in the female mouse (CD-1 and Swiss albino), hemangiosarcoma in the male CD-1 mouse, kidney tumours in the male CD-1 mouse and SD rat, liver adenoma in the male rat (SD and Wistar), malignant lymphoma in the male and female CD-1 mouse, skin basal cell tumour in the male SD rat and skin keratoacanthoma in male rats (SD and Wistar). Some evidence (SE) for a causal relationship was put forth for kidney tumours in the male Swiss albino mouse, mammary tumours in the female Wistar rat, malignant lymphoma in the male and female Swiss albino mouse, pituitary adenoma in the male and the female Wistar rat, and testicular interstitial cell tumours in the male SD rat.

After thorough analysis and considering all factors that are important in the interpretation of cancer studies none of the tumours identified by the author as indicating clear evidence (CE) or some evidence (SE) of

carcinogenicity were found relevant. Most of the tumours selected by the author were previously dismissed by the EU experts as not relevant even before the last review of glyphosate in 2017, and the applicant believes that there is no solid toxicological evidence for glyphosate exposure related carcinogenicity in the mouse and the rat that warrants any science-based concerns for human health. The discussion of each of the suspect tumours is given below.

Clear evidence (CE) for carcinogenicity:

Adrenal cortical carcinoma in the female SD rat (Stout and Ruecker study):

The tumour incidences were 0/60, 0/60, 0/60, 3/60 at 0, 113, 457, and 1183 mg/kg bw/day, respectively. This tumour has not been considered treatment related by the authors of the study. There is no dose-related increase in adrenal cortical adenoma (1/60, 3/60, 2/60, 1/60), no dose-related increase in pre-neoplastic lesions and this tumour was not found in the males of the same study or in other rat studies. Therefore, this tumour has been considered not relevant for the risk assessment of glyphosate and was not discussed further in the previous EU review of glyphosate.

Hemangioma in female CD-1 mice (Sugimoto study):

In the Sugimoto study hemangiomas were observed in different tissues:

- In liver with an incidence of 0/50, 0/50, 1/50, 1/50;
- In the ovary with an incidence of 0/50, 0/50, 0/50, 1/50;
- In the uterus with an incidence of 0/50, 0/50, 1/50, 2/50;
- In the spleen with an incidence of 0/50, 0/50, 1/50, 0/50;
- In the abdominal cavity with an incidence of 0/8, 0/9, 0/9, 1/9;

At 0, 153.2, 786.8, and 4116 mg/kg bw/day, respectively. Taken together as systemic tumours a significant positive trend is obtained. However, hemangiomas have also been observed in males (liver and testes) but without any dose-response relationship and the highest incidence found was in the control group (1/50). These tumours have not been confirmed in the other carcinogenicity studies in the CD-1 mouse. Moreover, the dose level (4116 mg/kg bw/day) at which the incidence was statistically significantly increased when compared against the control, is more than 4-fold the limit dose for the testing of carcinogens in rodent species. If that dose is ignored there is no significative positive trend. Therefore, this tumour has been considered not relevant for the risk assessment of glyphosate and was not discussed further in the previous EU review of glyphosate.

Hemangioma in female Swiss albino mice (Kumar study):

In the re-analysis of the tumour data of the Kumar study by K. Weber (report submitted in 2017) no statistically significant trend was found for systemic neoplasms using the Peto test. When analyzed using the Fischer's exact test no statistically significant increase in incidence was found in pair-wise comparisons of all dose groups with the control group. It is important to emphasize that this study was compromised by non-identified ecto-and endoparasites in a large number of animals. Therefore, this tumour has been considered not relevant for the assessment of glyphosate.

Hemangiosarcoma in the male CD-1 mouse (Atkinson study):

The tumour incidences were 0/50, 0/50, 0/50, 4/50 (3 in liver and 1 in prostate) at 0, 98, 297, and 988 mg/kg bw/day, respectively. The incidence at the highest dose (8 %) was still within the historical control range of the test laboratory (0-8 %, 300 male mice in 6 studies up to 1993). This tumour was not confirmed in other mouse studies of which one (Knezevich and Hogan study) with a dose level nearly 5-fold that of the

Atkinson study (4841 mg/kg bw/day). Therefore, this tumour has been considered not relevant for the assessment of glyphosate.

Kidney tumours in the male CD-1 mouse (Takahashi study, as reported by JMPR, 2016):
Renal cell adenoma (3/50) and renal cell carcinoma (1/50) were observed in males at 7470 mg/kg bw/day, but, according to the authors, there was no statistically significant difference with the control group. It is of note that the high dose considered in this study for males is extraordinarily high, more than 7-fold the limit dose for the testing of carcinogens in rodent species. If this dose is ignored there is no significant positive trend. These tumours were re-examined by the original study pathologist in 2012 because the Pesticide Expert Panel of the Food Safety Commission of Japan requested more information on historical control data and association with the non-neoplastic renal findings. After re-examination, the incidences for renal cell adenoma were 1/50, 1/50, and 1/50 at 167.6, 685, and 7470 mg/kg bw/day, showing no dose-response relationship. The incidence for renal cell carcinoma was confirmed to be 1/50 at 7470 mg/kg bw/day. The historical control data for the Takahashi study were not available, but the historical control values described in the re-examination document for renal cell carcinoma were 1/725 (0.13 %) in males and 0/725 (0 %) in females and for renal cell adenoma were 3/564 (0.53 %) in males and 0/564 (0 %) in females. The re-examination report also provides reference data of 0-1.8 % in males and 0 % for all doses in females for renal cell carcinoma, and 0-1.8 % in males and females for renal cell adenoma. The results of the re-examination revealed also that the tubular epithelial cell hypertrophy was localized with an incidence in each treatment group that did not significantly differ from that in the control group. There was no association between the tubular epithelial cell hypertrophy and the development of renal tumours. The renal cell tumours observed in this study are thus not relevant for the human risk assessment of glyphosate because (1) the incidence of renal tumours in males at 7470 mg/kg bw/day did not significantly differ from that in the control group upon re-evaluation; (2) none of the females had neoplastic or non-neoplastic lesions; and (3) the high dose considered in this study for males is more than 7-fold the limit dose for the testing of carcinogens in rodent species. Therefore, this tumour has been considered not relevant for the assessment of glyphosate.

Kidney tumours in the male SD rat (Enemoto study):
The incidences of kidney adenoma were 0/76, 0/75, 0/80, 4/78 at 0, 104, 354, and 1127 mg/kg bw/day. An increasing trend in the incidence of adenomas in the kidney was observed in males of the high dose group (animal 193: killed in extremis at week 92, animal 167: found dead at week 94, animal 159: found dead at week 101, and animal 169: killed by design after 104 weeks of treatment) and this incidence was greater than the historical control range referred to in the study report (0-2.9 %). However, according to the authors of this study, the increase observed was not statistically significant. No kidney tumours were found in the females and nearly all male rats at all dose levels suffered from chronic nephropathy (62/76, 63/75, 56/80, 67/78). This tumour in this study was not considered relevant for the risk assessment of glyphosate and was not discussed further in the previous EU review of glyphosate.

Hepatocellular adenomas in the male SD rat (Stout and Ruecker study):
The tumour incidences for adenomas were 3/60, 2/60, 3/60, 8/60 and of carcinomas were 3/60, 2/60, 1/60, 2/60 at 0, 89, 362, and 940 mg/kg bw/day, respectively. The incidence of adenomas at the high dose (13.3 %) is still within the historical control range of the test laboratory (1.4-18.3 %). Foci of cellular alteration were observed at all dose levels without any dose-response relationship and there were no signs of hepatocellular hypertrophy, a prerequisite for hepatocellular carcinogenesis. Beside the Brammer study no increase in hepatocellular adenomas was noted in the other rat studies. Therefore, this tumour was not considered relevant for the assessment of glyphosate.

Hepatocellular adenomas in the male Wistar rat (Brammer study):
The tumour incidences were 0/64, 2/64, 0/64, 5/64 at 0, 121, 361, 1214 mg/kg bw/day, respectively. The positive trend is significant and the incidence at the high dose is significantly different from the control. However, the incidence at the high dose (7.8 %) is still within the historical control range of the test laboratory (0-11.5 %, 26 studies in 1984-2003). There were no histopathological signs of liver enzyme induction or pre-neoplastic lesions. The high dose animals in this study survived longer when compared to the other groups. This may also influence the spontaneous tumour rate. Beside the Stout and Ruecker study no increase in hepatocellular adenomas was noted in the other rat studies. Therefore, this tumour was not considered relevant for the assessment of glyphosate.

Malignant lymphoma in the male CD-1 mouse (Sugimoto study):
The tumour incidences were 2/50, 2/50, 0/50, 6/50 at 0, 165, 838, 4348 mg/kg bw/day, respectively. The positive trend is significant but the incidence at the high dose is not significantly different from the control. Moreover, the incidence at the high dose (12 %) is still within the historical control range of the test laboratory (3.6-19.2 %, 458 male mice in 12 studies in 1993-1998). The trend has been found significantly positive because of the elevated incidence at a dose level that is over 4-fold the limit dose for carcinogenicity studies in rodents. If this dose is ignored the trend is not positive. Therefore, this tumour was not considered relevant for the assessment of glyphosate.

Malignant lymphoma in the female CD-1 mouse (Takahashi study):
The tumour incidences were 3/50, 1/50, 4/50, 6/50 at 0, 93.2, 909, and 8690 mg/kg bw/day, respectively. The increased incidence of lymphoma at the high dose was statistically significant in the trend test but not in a pairwise comparison. The trend has been found significantly positive because of the elevated incidence at an extraordinarily high dose level, more than 8-fold the limit dose for carcinogenicity studies in rodents. If this dose is ignored the trend is no longer significant. Therefore, this tumour was not considered relevant for the assessment of glyphosate.

Skin basal cell tumour in the male SD rat (Enemoto study):
The tumour incidences were 0/78, 0/75, 0/80, 3/78 for adenoma and 0/78, 0/75, 0/80, 1/78 for carcinoma at 0, 104, 354, and 1127 mg/kg bw/day. No increased incidence of this tumour was observed in the females or other rat studies and may be associated with other skin lesions (follicular hyperkeratosis and/or folliculitis/follicular abscess) observed in this study. Although there is a significant positive trend for the adenomas, the increase in incidence at the high dose level was not considered relevant for the risk assessment of glyphosate by the authors of this study. This tumour was not discussed further in the previous EU review of glyphosate.

Skin keratoacanthoma in the male SD rat (Stout and Ruecker study):
The tumour incidences were 1/60, 3/60, 4/60, 5/60 at 0, 89, 362, and 940 mg/kg bw/day. Although there is a significant positive trend the incidence at the high dose was not statistically significantly different from the control and considered not related to treatment. Skin keratoacanthoma is one of the most common spontaneous benign neoplasms in male Sprague Dawley rats. Therefore, this tumour was not considered relevant for the risk assessment of glyphosate by the authors of this study. This tumour was not discussed further in the previous EU review of glyphosate.

Skin keratoacanthoma in the male SD rat (Atkinson study):
The combined incidences of intracutaneous cornifying epithelioma (keratoacanthoma) were 1/50, 2/25, 0/19, 0/21, 5/50 at 0, 11, 112, 320, and 1147 mg/kg bw/day. Although the trend was significant, the incidence at the high dose was not statistically significantly different from the control and considered not related to treatment by the authors of this study. Skin keratoacanthoma is one of the most common spontaneous benign neoplasms in male Sprague Dawley rats. This tumour was not discussed further in the previous EU review of glyphosate.

Skin keratoacanthoma in the male SD rat (Enemoto study):
The incidences of the tumour were 4/76, 3/75, 0/80, 7/78 at 0, 104, 354, and 1127 mg/kg bw/day. The increased incidence of this skin tumour at the high dose may be associated with other skin lesions (follicular hyperkeratosis and/or folliculitis/follicular abscess) observed in this study. Although there is a significant positive trend for this tumour, the increase in incidence at the high dose level was not statistically significantly different from the control. Skin keratoacanthoma is one of the most common spontaneous benign neoplasms in male Sprague Dawley rats and considered by the authors of this study not relevant for the risk assessment of glyphosate. This tumour was not discussed further in the previous EU review of glyphosate.

Skin keratoacanthoma in the male Wistar rat (Wood study):
There were no treatment-related conditions seen in the skin or in subcutaneous tissues, but several spontaneous lesions were observed. Epidermal ulceration and scab formation, inflammatory lesions, abscess formation, focal acanthosis, focal mineralisation, focal dermal thickening, and focal necrosis were seen, occasionally or rarely and without significance. This tumour was not discussed further in the previous EU review of glyphosate.

Some evidence for carcinogenicity (SE)
Kidney tumours in the male Swiss albino mouse (Kumar study):
In the re-analysis of the tumour data of the Kumar study by K. Weber (submitted in 2017) no statistically significant trend was found for systemic neoplasms in the Peto test. When analyzed using the Fischer's exact test no statistically significant increase in incidence was found in pair-wise comparisons of all dose groups with the control group. It is important to emphasize that this study was compromised by non-identified ecto-and endoparasites in a large number of animals. Therefore, this tumour was not considered relevant for the assessment of glyphosate.

Mammary tumour in the female Wistar rat (Wood study):
At interim and terminal sacrifice combined mammary neoplasia was seen in 6 female mice. There were no mammary neoplasms in the control group but carcinomas were seen with incidences of 2/51, 3/51, and 1/51 at 153.2, 786.8, and 4116 mg/kg bw/day, respectively. All neoplasms were adenocarcinomas with the exception of one adenosquamous carcinoma seen in a low dose group animal. No increase in the incidence of these tumours was reported in the females of other rat studies. The authors concluded that there was no effect of treatment upon the incidence of mammary neoplasia in this study. Therefore, this tumour was not considered relevant for the assessment of glyphosate.

Malignant lymphoma in the male Swiss albino mouse (Kumar study):
In the re-analysis of the tumour data of the Kumar study by K. Weber (2017) no statistically significant trend was found for systemic neoplasms in the Peto test. When analyzed using the Fischer's exact test no statistically significant increase in incidence was found in pair-wise comparisons of all dose groups with

the control group. It is important to emphasize that this study was compromised by non-identified ecto-and endoparasites in a large number of animals. Therefore, this tumour was not considered as relevant for the assessment of glyphosate.

Pituitary adenomas in the male and the female Wistar rat (Wood study):
Pituitary adenomas were only seen in female mice with incidences of 0/51, 1/51, 0/51, 2/52 at 0, 104.5, 348.6, and 1381.9 mg/kg bw/day. The group distribution was unrelated to treatment. Therefore, this tumour was not considered relevant for the assessment of glyphosate.

Testicular interstitial cell tumour in the male SD rat (Lankas study):
The incidences of this tumour were 0/50, 3/50, 1/50, 6/50 at 0, 3.05, 10.30, and 31.49 mg/kg bw/day, respectively. The positive trend is statistically significant and the incidence at the high dose level (12 %) is statistically significantly different from the control and greater that the historical control rate of the test laboratory (3.4-6.6 %). However, there was no dose-response relationship for interstitial cell hyperplasia (1/50, 1/50, 1/50, 0/50). Since the dose range considered in this study (0-31.5 mg/kg bw/day) is approximately at least 30-fold lower than that of all the other studies in rats where no increase of such tumours was found this finding should be considered as spontaneous in nature. Therefore, this tumour was not considered relevant for the risk assessment of glyphosate and was not discussed further in the previous EU review of glyphosate.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because some of the statistical methods employed were not described in sufficient detail. Besides, the results of this study are not in agreement with the findings of Crump *et al*. 2020 in relation to the estimation of false positives and the overall evaluation of the significance of the tumours by the EU regulatory authorities. All the tumours that were identified by the author as providing clear evidence for the carcinogenicity of glyphosate have been previously dismissed in the EU regulatory process.

Edition No.: M-812283-01-1

Author	Wozniak Ewelina Reszka Edyta; Jablonska Ewa Balcerczyk Aneta Broncel Marlena Bukowska Bozena
Source	Toxicology in vitro : an international journal published in association with BIBRA, (2019 Nov 18) Vol. 63, pp. 104736. Electronic Publication Date: 18 Nov 2019 Journal code: 8712158. E-ISSN: 1879-3177. L-ISSN: 0887-2333.
Title	Glyphosate affects methylation in the promoter regions of selected tumor suppressors as well as expression of major cell cycle and apoptosis drivers in PBMCs (in vitro study).
Publication Year	2019
Accession Number	2021815981 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
The objective was to assess epigenetic mechanisms of action of glyphosate in human PBMCs, which has been poorly studied in cellular models including blood cells. The study was conducted using an in vitro test system. The ability of glyphosate to impact the measured parameters was demonstrated (global DNA methylation of PBMCs, methylation in the promoter regions of selected tumor suppressors (P21 and TP53), and expression of major cell cycle and apoptosis drivers (P16, TP53, BCl2, CCND1 and P21). However, a positive control was not used, and a clear dose-response was not established for all of the measured parameters. Additionally, the measured effects in vitro are not clearly linked to an adverse outcome in vivo. While it is stated that the concentrations used are comparable to environmental exposure, external exposure was not linked to a corresponding internal concentration. Therefore, it is not possible to calculate a dose for risk assessment purposes. The study is useful for supplemental information on in vitro effects resulting from glyphosate exposure, but, is not appropriate for derivation of an endpoint in human health risk assessment.

This publication is considered relevant and reliable without restrictions because the assays conducted comply in general with the quality criteria for in vitro testing.

Edition No.: M-812160-01-1

Author	Biserni Martina; Mesnage Robin; Ferro Raquel; Antoniou Michael N Wozniak Eva; Xenakis Theodoros; Mein Charles A Wozniak Eva; Xenakis Theodoros; Mein Charles A
Source	Toxicological sciences : an official journal of the Society of Toxicology, (2019 Apr 17) . Electronic Publication Date: 17 Apr 2019 Journal code: 9805461. E-ISSN: 1096-0929. L-ISSN: 1096-0929.
Title	Quizalofop-p-Ethyl Induces Adipogenesis in 3T3-L1 Adipocytes.
Publication Year	2019
Accession Number	2021155829 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
In this study glyphosate, among other pesticide active substances, were investigated for their effect on lipid accumulation in differentiated adipocytes in vitro at concentrations ranging from 0.1 to 1000 µM. The results indicated that at the concentrations tested, glyphosate scored negative for lipid accumulation. This publication is considered relevant for the risk assessment of glyphosate and reliable without restrictions.

Edition No.: M-812504-01-1

Author	Crump Kenny
Source	Risk analysis : an official publication of the Society for Risk Analysis, (2019 Dec 30) . Electronic Publication Date: 30 Dec 2019 Journal code: 8109978. E-ISSN: 1539-6924. L-ISSN: 0272-4332.
Title	The Potential Effects of Recall Bias and Selection Bias on the Epidemiological Evidence for the Carcinogenicity of Glyphosate.
Publication Year	2020
Accession Number	2021952890 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

It is well known that recall bias is a potentially important bias in cancer case control studies where study participants are asked to recall their past exposures. In an ideal study, information about exposures for cases and controls would be collected under exactly the same circumstances. However, circumstances are quite different for cases and controls. Cancer cases have suffered a grievous illness and it is only natural for them to be deeply introspective about what might have caused their cancers. Controls have no such motivation that would augment their recall (or reporting). So, the concern expressed in many textbooks is that recall bias tends to produce false positive results. The purpose of this analysis by Crump was to evaluate the evidence for recall bias in the overall pattern of results in five case control studies and two cohort studies that comprise the main part of the glyphosate-NHL literature.

In evaluating the case control studies, Crump reasoned that the percentage of odds ratios > 1 for non-glyphosate exposures should be approximately 50 % if recall bias was not operative and those exposures did not cause NHL. Yet, it turned out that the percentages of ORs >1 for non-glyphosate exposures were 90 % for Hardell et al. (2002), 90 % for Erikson et al. (2008), 93 % for McDuffie et al. (2001), 76 % for Orsi et al. (2009), and 53 % for DeRoos et al. (2003). These extreme departures from 50 % for 4 of the 5 case control studies is consistent with recall bias, perhaps augmented by a type of selection bias in the analyses by Hardell et al. (2002) and Eriksson et al. (2008). In contrast, in the most recent publication from the Agricultural Health Study (Andreotti et al. 2018), only 48 % of the relative risks (RR) calculated were >1 – a percentage in the range expected with a true probability of 50 %. While the evaluation of Andreotti et al. (2018) concerned glyphosate and other cancer sites and not other exposures and NHL, the principle is the same: under the null hypothesis the proportion of ORs or RRs > 1 should be roughly 50 % absent bias.

We agree with Crump's conclusion that the 4 case-control studies with a high proportion of ORs > 1 are "contaminated" by statistical bias and are not reliable as evidence of a relationship between glyphosate and NHL. Of course, there are also other types of bias that may contribute to the high proportion of positive ORs (e.g. lack of control for confounding, lower participation for controls than cases (traditional selection bias), proxy respondents, etc.) (see Acquavella et al. 2016). Nonetheless, Crump's point is well taken that ORs for glyphosate in 4 of the 5 case control studies should be interpreted as unreliable because the vast majority of ORs for other exposures are >1.

Edition No.: M-813477-01-1

Author	Duforestel Manon; Nadaradjane Arulraj; Bougras-Cartron Gwenola; Briand Josephine; Olivier Christophe; Frenel Jean-Sebastien; Vallette Francois M; Cartron Pierre-Francois Duforestel Manon; Nadaradjane Arulraj; Bougras-Cartron Gwenola; Briand Josephine; Oli
Source	Frontiers in genetics, (2019) Vol. 10, pp. 885. Electronic Publication Date: 27 Sep 2019 Journal code: 101560621. ISSN: 1664-8021. L-ISSN: 1664-8021. Report No.: PMC-PMC6777643.
Title	Glyphosate Primes Mammary Cells for Tumorigenesis by Reprogramming the Epigenome in a TET3-Dependent Manner.
Publication Year	2019
Accession Number	2021678139 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The objective of this study was to investigate DNA hypomethylation in MCF10A cells, tumorigenic response for MCF10A Cells in a two-factor hit model, prevention of tumor formation in glyphosate-challenged cells, and TET3-Mediated Gene Demethylation following glyphosate exposure. This study was conducted in vitro using only one level of glyphosate. Glyphosate was not correlated to environmental exposures. In the in vivo portion of the study, a sufficient number of animals were not used to determine a carcinogenic response for statistical analysis. While this study is acceptable as supplemental information on the in vitro effects of glyphosate, it is not appropriate for endpoint derivation in human health risk assessment.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate used was insufficiently characterized and only one and extremely low concentration of glyphosate was used.

Edition No.: M-813469-01-1

Author	Pahwa Manisha Beane Freeman Laura E; Spinelli John J; Blair Aaron; McLaughlin John R; Zahm Shelia Hoar; Cantor Kenneth P; Weisenburger Dennis D; Punam Pahwa Punam Pahwa; Dosman James A; Demers Paul A; Harris Shelley A
Source	Scandinavian journal of work, environment & health, (2019 Jun 27) . Electronic Publication Date: 27 Jun 2019 Journal code: 7511540. E-ISSN: 1795-990X. L-ISSN: 0355-3140.
Title	Glyphosate use and associations with non-Hodgkin lymphoma major histological sub-types: findings from the North American Pooled Project.
Publication Year	2019
Accession Number	2021314446 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The main advantage of this pooled analysis compared with the previously published individual studies was to enable a more comprehensive analysis for glyphosate with regard to confounding factors and proxy respondents. In general, adjusting for use of 2,4-D, dicamba, and malathion reduced ORs for glyphosate. Analyses that excluded proxy respondents were generally similar to analyses that included them, though there were some instances, specifically for other NHL subtypes, where excluding proxies appreciably reduced the adjusted OR.

Left unaddressed in this pooled analysis is the intractable issue of case-recall bias in case control studies. Crump has shown in an analysis of all the case control studies that have reported ORs for glyphosate, including the studies in this pooled analysis, that results for all pesticides were markedly skewed toward positive associations (Crump K, Risk Analysis DOI: 10.1111/risa.13440). Crump noted particularly that the ORs for individual pesticides in the McDuffie et al. study (and 2 other studies not included in this pooled analysis) were nearly all greater than 1.0. He considered this evidence of case recall bias. Fundamentally, using self-reported exposure recollections from cases and controls violates the basic principle that data should be collected under equivalent circumstances for the groups to be compared (viz., cases and controls). That is impossible when pesticide recall is likely to be affected by their grievous illness for cases and not for controls. Accordingly, while this pooled analysis is an advance in understanding confounding by other pesticides and in assessing the impact of reporting by proxies (except in analysis where 50 % of the subjects were excluded due to data limitations) in the 2 included studies, systematic error related to case recall bias remains an outstanding issue for interpreting the results for glyphosate.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because it concerns a pooled case control study which is subject to recall and selection bias. Notably, potential case-recall bias remains an unresolved issue in this pooled reanalysis.

Edition No.: M-813471-01-1

Author	Wang Lei; Deng Qipan; Hu Hui; Liu Ming; Gong Zhaojian; Zhang Shanshan; Ma Xiaodong; Li Yong Wang Lei Hu Hui; Lu Zhongxin Liu Ming Gong Zhaojian Zhang Shanshan Xu-Monette Zijun Y; Young Ken H Ma Xiaodong Ma Xiaodong
Source	Journal of hematology & oncology, (2019 Jul 05) Vol. 12, No. 1, pp. 70. Electronic Publication Date: 5 Jul 2019 Journal code: 101468937. E-ISSN: 1756-8722. L-ISSN: 1756-8722.
Title	Glyphosate induces benign monoclonal gammopathy and promotes multiple myeloma progression in mice.
Publication Year	2019
Accession Number	2021345783 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The objective of this study was to investigate the pathogenic role of glyphosate in multiple myeloma using Vk*MYC mice. The study did demonstrate the ability of glyphosate to impact measured parameters in the tested models. However, this study is not appropriate for human health risk assessment. The number or animals per group was below the recommended number for guideline toxicity studies and to perform sufficient statistical analysis. Only one dose level was used in the chronic study. It was not possible to correlate effects with a glyphosate dose-response as the water consumption (and therefore test substance intake) of animals was not provided and it is therefore impossible to calculate a dose on a mg/kg bw basis for risk assessment.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate used was not characterized, only one dose was considered for the chronic study and the number of animals used per group was either too low (acute study) or not reported (chronic study).

Edition No.: 2018_885014_-_STN_Database.8827421

Author	Andreotti, Gabriella; Koutros, Stella; Hofmann, Jonathan N.; Lerro, Catherine C.; Silverman, Debra T.; Freeman, Laura E. Beane (Reprint) Lubin, Jay H. Alavanja, Michael C. Sandler, Dale P.; Parks, Christine G. Lynch, Char
Source	JNCI-JOURNAL OF THE NATIONAL CANCER INSTITUTE, (MAY 2018) Vol. 110, No. 5, pp. 509-516. ISSN: 0027-8874.
Title	Glyphosate Use and Cancer Incidence in the Agricultural Health Study
Publication Year	2018
Accession Number	2018:885014 SCISEARCH
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The AHS is an ongoing prospective cohort study of glyphosate and other pesticides. It was initiated in 1993 and has been ongoing for more than 25 years. Researchers from the US National Cancer Institute and other government agencies initiated the AHS as a prospective cohort study to eliminate the possibility of case-recall bias – an intractable potential bias in case control studies that rely on self-reported exposure information. Crump (Risk Analysis DOI:10.1111/risa.13440) has recently illustrated that the results from the glyphosate case-control studies align closely with what would be expected from case recall bias.

In addition to obviating concerns about case-recall bias, the Andreotti et al. publication is noteworthy on several counts. First, the frequency of glyphosate use by participants (median = 48 days, IQR 20 to 166 days) vastly exceeds that in the glyphosate case-control studies. In those studies the most frequent days of use category is > 10 days (Eriksson M, et al. Int J Cancer. 2008; 123:1657-1663), while most of the case control studies' primary analyses were based on 1 day or more of use in a lifetime. Second, the participants in the AHS were licensed pesticide applicators who were considered by the authors to be very capable to report pesticide use accurately compared with other study populations. Third, the analyses by Andreotti et al. controlled for a multitude of personal factors and for other pesticides in addition to incorporating a wide range of sensitivity and lagged analyses (allowing for up to 20+ years induction-latency). No other study has evaluated the relationship between glyphosate use and cancers as extensively. The AHS is, by far, the most informative and relevant study epidemiologic study for glyphosate to date. The authors found no evidence of an association between glyphosate use and risk of any solid tumour, NHL, or multiple myeloma.

Accordingly, given the AHS results for NHL among those with extensive glyphosate use (n = 111 exposed cases, RR = 0.9, 95 % CI 0.6 – 1.2), it is unlikely that the positive associations for glyphosate and NHL in some case control studies are valid. As follow-up of the AHS cohort continues, it remains to be seen whether subsequent results will identify relationships between individual cancers and glyphosate use that are relevant for risk evaluations.

Edition No.: M-813113-01-1

Author	Presutti, Roseanna; Harris, Shelley A. (correspondence); Kachuri, Linda; Pahwa, Manisha Presutti, Roseanna; Harris, Shelley A. (correspondence); Kachuri, Linda; Pahwa, Manisha Harris, Shelley A. (correspondence); Kachuri, Linda; McLaughlin, John R. Harris
Source	International Journal of Cancer, (15 Oct 2016) Vol. 139, No. 8, pp. 1703-1714. Refs: 44 ISSN: 0020-7136; E-ISSN: 1097-0215 CODEN: IJCNAW
Title	Pesticide exposures and the risk of multiple myeloma in men: An analysis of the North American Pooled Project.
Publication Year	2016
Accession Number	20160592154 EMBASE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
Four population-based incident case-control studies (3 US studies and one Canadian study) pooled in the North American Pooled Project (NAPP) aimed to investigate the effects of pesticides and other agricultural exposures on the risk of lymphatic and hematopoietic cancers. The present analysis is restricted to a subset of three NAPP studies (Iowa, Nebraska and Canada) where multiple myeloma (MM) cases were recruited. Self-reported information on pesticide use, farming activities and demographic characteristics was collected and the odds ratios (OR) were calculated for “ever/never” exposure, years of exposure and cumulated lifetime days of exposure to glyphosate with and without exclusion of proxy respondents. The result is that no statistically significant increases in risk of multiple myeloma (MM) associated with self-reported exposure to glyphosate were observed.

This publication is considered relevant for glyphosate risk assessment but reliable with restrictions because it concerns pooled case control studies which are subject to recall bias and in which confounding factors could not be ruled out.

Edition No.: M-813221-01-1

Author	Sorahan Tom
Source	International journal of environmental research and public health, (2015 Jan 28) Vol. 12, No. 2, pp. 1548-59. Electronic Publication Date: 28 Jan 2015 Journal code: 101238455. E-ISSN: 1660-4601. L-ISSN: 1660-4601. Report No.: NLM-PMC4344679; PMC-PMC43446
Title	Multiple myeloma and glyphosate use: a re-analysis of US Agricultural Health Study (AHS) data.
Publication Year	2015
Accession Number	2015516552 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
In this study the relative risk estimates for exposed and non-exposed applicators were calculated using Poisson regression and subjects with missing data were not excluded from the main analyses. When using the full dataset adjusted for age and gender the analysis produced a RR close to unity for ever-use of glyphosate. Additional adjustment for lifestyle factors and use of ten other pesticides had little effect. This study found no statistically significant trends of multiple myeloma risk with reported cumulative days of glyphosate use and unexceptional point estimates of risk for ever-use of glyphosate. This was irrespective of whether the analyses had adjustment for a few basic variables (age and gender) or adjustment for many other lifestyle factors or pesticide exposures, as long as data on all available pesticide applicators were used. The suspiciously elevated RRs reported previously arose from the use of restricted data sets that, probably by chance, turned out to be unrepresentative.

This publication concerns a secondary analysis of the data from the Agricultural Health Study (AHS) and is considered relevant for the risk assessment of glyphosate and reliable without restrictions because it complies with the reliability criteria of a well conducted epidemiology study.

Edition No.: M-813569-01-1

Author	Gorga Agostina; Rindone Gustavo Marcelo; Centola Cecilia Lucia; Pellizzari Eliana Herminia; Camberos Maria Del Carmen; Riera Maria Fernanda; Galardo Maria Noel; Meroni Silvina Beatriz Sobarzo Cristian M Marin-Briggiler Clara Isabel; Cohen Debora J
Source	Frontiers in endocrinology, (2021) Vol. 12, pp. 615678. Electronic Publication Date: 11 Mar 2021 Journal code: 101555782. ISSN: 1664-2392. L-ISSN: 1664-2392. Report No.: PMC-PMC7992013.
Title	Low Doses of Glyphosate/Roundup Alter Blood-Testis Barrier Integrity in Juvenile Rats.
Publication Year	2021
Accession Number	2023832455 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The aim of the study was to investigate the possible effects of glyphosate (G) or the commercial formulation Roundup (R) treatment of juvenile male rats on blood-testis barrier function and on adult male sperm production. Pups were randomly assigned to the following groups: control group (C), receiving water; G2 and G50 groups, receiving 2 and 50 mg/kg/day G respectively; and R2 and R50 groups receiving 2 and 50 mg/kg/day R respectively. Treatments were performed orally from postnatal day (PND) 14 to 30, period of life that is essential to complete a functional blood-testis barrier. Evaluation was done on PND 31.
In conclusion, the results presented show that continuous exposure to low doses of G or R alters blood-testis barrier permeability in juvenile rats, but have no effect on clinical chemistry parameters, intertesticular testosterone levels, androgen receptor expression, or testis weight. Furthermore, adult animals treated during the juvenile stage showed no differences in daily sperm production compared with control animals, demonstrating that blood-testis barrier effects are a transient, reversible phenomenon.

The article is considered relevant (Category A) and reliable with restrictions for the following reason:
Purity missing for glyphosate technical, exact number of animal/group difficult to find, no dose-response relationship, no HCD, and no positive control to confirm assay validity.

Edition No.: M-813522-01-1

Author	Refaie, Amel A. Ramadan, Amal (correspondence) Aly, Hanan F.
Source	Current Topics in Pharmacology, (December 2020) Vol. 24, pp. 69-76. Refs: 41 ISSN: 0972-4559
Title	Hematological, biochemical, antioxidant and histopathological alterations in kidneys of wistar rat pups exposed to glyphosate herbicide during lactation period.
Publication Year	2020
Accession Number	20210122036 EMBASE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The aim of this study was to evaluate the effects of glyphosate administered orally to the dams during lactation period of pup rats at a daily dose of 0.3 mg/kg body weight (acceptable daily intake ADI), 31 mg/kg body weight (no observed adverse effect level NOAEL) and 56 mg/kg body weight (1/100 LD50) for 21 days. However, the underlying assumption of glyphosate transfer to pups via milk is not supported by the data – this is well explained in mammals including humans (Bus, 2015*; McGuire et al, 2016**). At the end of the treatment, the suckling pups were separated into male and female, and the relative kidney weights were measured. The levels of creatinine and urea were determined in serum. Oxidative stress was measured using lipid peroxidation and the activities of glutathione peroxidase (GPx) and catalase (CAT) in kidney tissue were also measured. Test substance administration in this study was to two pregnant rats per group, and thus the experimental unit is the litter, not all the individual pups across two litters with the same dose. Therefore, in contrast to the statistical analyses presented, there are only two experimental units (litters) per dose group (2-1 = 1 degree of freedom; **not** 10-1 = 9 d.f.), which lacks adequate statistical power for meaningful analysis in both the ANOVA and LSD test.

The pups showed increased relative kidney weight with the highest increment in 1/100 LD50 dose followed by NOAEL and ADI doses. Also, marked increment in malondialdehyde (MDA) level along with significant inhibition in catalase (CAT) and glutathione peroxidase (GPx) activities were detected in pup's kidney tissues. Counts of WBCs and RBCs and Hb content exhibited significant reduction in the blood of pups that received 1/100 LD50 dose which is more than the NOAEL and ADI doses. Histopathological examinations of kidney tissue demonstrated focal fibrosis with inflammatory cells between glomeruli and tubules of male and female pup kidney tissue (lower scoring severity (+) in ADI and NOAEL doses than 1/100 LD50 (+++)). Additionally, at 1/100 LD50 dose focal haemorrhages, degradation in tubular lining epithelial cells (+) and renal arteries congestion (++) were observed. These results for F1 kidney weights and histopathology data are not consistent with the weight of evidence across in numerous

multigenerational studies up to the limit dose of 1000 mg/kg bw/day.

The article is considered relevant (Category A) and reliable with restrictions for the following reasons: No method of analysis, no HCD, and inappropriate statistical assumptions on the experimental unit.

References:

*Bus, J. S. (2015). Analysis of Moms Across America report suggesting bioaccumulation of glyphosate in U.S. mother's breast milk: Implausibility based on inconsistency with available body of glyphosate animal toxicokinetic, human biomonitoring, and physico-chemical data. *Regulatory Toxicology and Pharmacology* (2015), Vol. 73, Issue, 3, pp. 758-64. doi: 10.1016/j.yrtph.2015.10.022.

**McGuire M. K. at al. (2016). Glyphosate and aminomethylphosphonic acid are not detectable in human milk. *The American Journal of Clinical Nutrition* (2016), Vol. 103, Issue 5, pp 1285-1290. https://doi.org/10.3945/ajcn.115.126854

Edition No.: M-813581-01-1

Author	Zhao Lijia; Zhang Jing; Yang Luda; Zhang Haisen; Zhang Yu; Gao Dengke; Jiang Haizhen; Li Yating; Dong Hao; Ma Tiantian; Wang Xiaoyu Wu Meina Wang Aihua Jin Yaping; Chen Huatao Yuan Yalin
Source	The Science of the total environment, (2021 Apr 25) Vol. 785, pp. 147323. Electronic Publication Date: 25 Apr 2021 Journal code: 0330500. E-ISSN: 1879-1026. L-ISSN: 0048-9697.
Title	Glyphosate exposure attenuates testosterone synthesis via NR1D1 inhibition of StAR expression in mouse Leydig cells.
Publication Year	2021
Accession Number	2024012619 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article hypothesize a mode of action to perturb testosterone synthesis via NR1D1 mediated inhibition of StAR expression in mouse Leydig cells.

This study examined the effects of glyphosate on the expression of the circadian clock and steroidogenic genes, as well as testosterone production in TM3 cells and primary LCs. The authors also investigated the effects of glyphosate on PER2::LUCIFERASE (PER2::LUC) oscillations in mouse primary LCs isolated from mPer2Luciferase (mPer2Luc) reporter gene knock-in mice. Furthermore, the effects of glyphosate exposure on the expression of core clock and steroidogenic genes in mouse testes as well as serum testosterone levels were determined in vivo. Finally, dual-luciferase reporter and EMSA assays were used to uncover the underlying molecular mechanism of glyphosate impairment of testosterone production involving NR1D1 regulation of StAR expression in LCs. The lack of a concurrent and historical positive control data substantially diminishes confidence in the predictability of the methodology employed to probe the proposed mechanism.

The results indicate that glyphosate perturbs testosterone synthesis via NR1D1 mediated inhibition of StAR expression in mouse LCs. These results contradict a large body of high-quality data assessing endocrine disruption and specifically steroidogenesis. Furthermore, the results and conclusions of this publication are not consistent with Levine et al. (2007), which specifically investigated glyphosate & formulation in mouse Leydig cells and StAR protein expression.

The article is considered relevant (Category A) and reliable with restrictions for the following reason:

No purity of the test material provided, no HCD/positive control reported. Only one dose evaluated/no dose-effect relationship for the in vivo experiment. The lack of a concurrent and historical positive control data substantially diminishes confidence in the predictability of the methodology employed to probe the proposed mechanism.

References:
Levine s. et al; Disrupting mitochondrial function with surfactants inhibits MA-10 Leydig cell steroidogenesis, Cell Biol Toxicol (2007) 23:385–400.

Edition No.: M-812508-01-1

Author	Gorga Agostina; Rindone Gustavo Marcelo; Centola Cecilia Lucia; Pellizzari Eliana Herminia; Camberos Maria Del Carmen; Cigorraga Selva Beatriz; Riera Maria Fernanda; Galardo Maria Noel Sobarzo Cristian Meroni Silvina Beatriz
Source	Toxicology in vitro : an international journal published in association with BIBRA, (2020 Feb) Vol. 62, pp. 104682. Electronic Publication Date: 15 Oct 2019 Journal code: 8712158. E-ISSN: 1879-3177. L-ISSN: 0887-2333.
Title	In vitro effects of glyphosate and Roundup on Sertoli cell physiology.
Publication Year	2020
Accession Number	2021692986 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
This in vitro investigation showed that exposure to G and R at 100 ppm alters Sertoli cell (SC) junction barrier permeability, measured by decreased TER, and also decreased testosterone-stimulated TER. This study also showed that, at least in part, the loss of location of claudin11 at the interface between neighboring Sertoli cells might be responsible for the disassembly of the barrier. G or R did not modify androgen receptor mRNA or protein levels, nor did G modify P-p38-MAPK and P-ERK1/2 signalling pathways involved with BTB integrity at any doses tested, or affect the expression of intercellular junction proteins (claudin11, occludin and ZO-1). However, G and R induced redistribution of claudin11 at the zone of contact between cells. Neither G nor R modified lactate production, glucose uptake, GLUT1, FA oxidation, or FAT/CD36 and CPT1 expression in SC, thus indicating no effect of G or R on SC nutritional function or metabolism.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate used was not sufficiently characterised, there was no positive control and most of the endpoints were tested at only 2 concentrations preventing any dose-response evaluations, with the highest concentration exceeding a physiologically relevant dose.

Edition No.: M-813462-01-1

Author	Manservisi Fabiana; Panzacchi Simona; Mandrioli Daniele; Falcioni Laura; Bua Luciano; Manservigi Marco; Belpoggi Fiorella Manservisi Fabiana; Spinaci Marcella; Galeati Giovanna Lesseur Corina; Swan Shanna H; Chen Jia Mandrioli Daniele Mantovani Alberto; L
Source	Environmental health : a global access science source, (20190312) Vol. 18, No. 1, pp. 15. Electronic Publication Date: 12 Mar 2019 Journal code: 101147645. E-ISSN: 1476-069X. L-ISSN: 1476-069X. Report No.: PMC-PMC6413565.
Title	The Ramazzini Institute 13-week pilot study glyphosate-based herbicides administered at human-equivalent dose to Sprague Dawley rats: effects on development and endocrine system.
Publication Year	2019
Accession Number	2020927606 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

In this pilot study the effect of glyphosate and its reference formulation Roundup Bioflow (MON 52276) at a dose of 1.75 mg glyphosate acid eq./kg bw/day on endocrine modulation was investigated in female rats during pregnancy and lactation, and in male and female rats during lactation, the peripubertal period and adulthood. The endpoints analysed were body weight, water and food consumption, gestational parameters, litter parameters, landmarks of sexual development, estrous cyclicity, gross and histopathology of reproductive and endocrine tissues, sperm parameters and serum and plasma hormone levels. MON 52276 exposure was associated with statistically significant increase of ano-genital distance in males and females, a delay of first estrous and increased serum testosterone in females and altered testosterone metabolism in both males and females. MON 52276 elicited more pronounced effects than glyphosate, which only increased statistically significantly anogenital distance during the peripubertal period. The statistically significant increase in TSH levels in glyphosate and MON 52276 treated rats was not associated with histopathological changes in the thyroid and thus of minor toxicological significance. The effect of glyphosate on ano-genital distance is not corroborated by any reproductive toxicity study where rats were exposed to much higher doses of glyphosate (> 1,000 mg/kg bw/day).

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because of the limited number of animals used per dose level and only one dose level tested.

Edition No.: M-812256-01-1

Author	Pham Thu Ha; Derian Lohann; Kervarrec Christine; Kernanec Pierre-Yves; Jegou Bernard; Smagulova Fatima; Gely-Pernot Aurore
Source	Toxicological sciences : an official journal of the Society of Toxicology, (2019 May 01) Vol. 169, No. 1, pp. 260-271. Journal code: 9805461. E-ISSN: 1096-0929. L-ISSN: 1096-0929.
Title	Perinatal Exposure to Glyphosate and a Glyphosate-Based Herbicide Affect Spermatogenesis in Mice.
Publication Year	2019
Accession Number	2020855679 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The effect of glyphosate exposure from the day of vaginal plug detection to 20 days post partum via the drinking water at concentrations corresponding with 0.5, 5 and 50 mg/kg bw/day on male reproductive parameters in mice of 5, 20 and 35 days old and 8 months old was investigated. The parameters measured were the number of spermatogonia and expression of genes important to testicular function in 5–day old mice, testicular histopathology in 20–day old mice, relative weight of testes, epididymis and seminal vesicles, epididymal sperm count, serum testosterone levels, GATA1 positive cell count and ZBTB16 positive cell count in 35–day old mice, and relative weight of testes, epididymis and seminal vesicles and serum testosterone levels in 8-month old mice. No statistically significant change was found for the number of spermatogonia in 5–day old mice. The only genes of which the expression was statistically significantly changed in a dose-related fashion were Bcl2 and Kit. In 20–day old mice, sperm depleted seminiferous tubules were noted at 5 mg/kg bw/day but not at 0.5 and 50 mg/kg bw/day glyphosate. In 35–day old mice there was no statistically significant change in the relative weight of the epididymis and the seminal vesicles, epididymal sperm count and GATA1 positive cell count. No dose-effect relationship could be established for relative weight of testes, serum testosterone levels and ZBTB16 positive cell count. In 8-month old mice no statistically significant change could be observed for relative weight of epididymis and seminal vesicles and serum testosterone levels. No dose-effect relationship could be established for the decrease in relative testes weight. From these data it can be concluded that there is no evidence that glyphosate dosed orally to mice up to 50 mg/kg bw/day during the perinatal period is an endocrine disruptor and has an adverse effect on testicular function and development. This has been corroborated by reproduction toxicicity studies with rats at much higher dose levels.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the test conditions were not clearly described and the number of animals tested per dose level is too limited.

Edition No.: M-812274-01-1

Author	Ren Xin; Dai Pengyuan; Perveen Aneela; Tang Qian; Zhao Liangyu; Jia Xiao; Li Yansen Li Chunmei
Source	Environmental pollution (Barking, Essex : 1987), (2019 Nov) Vol. 254, No. Pt A, pp. 112906. Electronic Publication Date: 20 Jul 2019 Journal code: 8804476. E-ISSN: 1873-6424. L-ISSN: 0269-7491.
Title	Effects of chronic glyphosate exposure to pregnant mice on hepatic lipid metabolism in offspring.
Publication Year	2019
Accession Number	2021441876 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The current study aimed to examine any effects on lipid metabolism in foetuses and pups following prenatal exposure to glyphosate or the glyphosate formulation, Roundup™. Ten pregnant female rats per group were exposed from gestation day 1 through 19 to drinking water containing either 0.5 % glyphosate, prepared using "pure" glyphosate (N-(phosphonomethyl) glycine), or 0.5 % glyphosate using an appropriate dilution of Roundup™. A similar group of animals were given distilled water and served as the control group. Five females per group were terminated on gestation day 19 for examination of foetuses, while the remaining dams were allowed to litter and maintain their litters to postnatal day 21. Offspring (2/sex/litter where possible) were selected on postnatal days 7 and 21 for evaluation. Foetal and offspring evaluations included liver histology, serum biochemistry, liver lipid concentration and gene expression analysis of genes related to lipid metabolism in the liver.

The study is non-GLP and does not report the following information;

- Purity of test items
- Body weight and clinical signs for pregnant animals
- Clinical observations of offspring
- Achieved dose of glyphosate in treated animals in mg/kg bw/day.
- Measures to control inter animal and intergroup variability such as
    - Time of necropsy distributed equally across groups
    - Standardisation of litter size on day 4 of lactation to mitigate variability caused by differences in liter size.
- More than a single dose level of glyphosate (0.5 % solution); thus, preventing dose-response characterisation
- Liver weight of foetuses or offspring
- Normal physiological ranges for serum and liver biochemistry in this strain of rat at this laboratory
- Clear reporting of statistical evaluation and differences
- Thorough histological evaluations of the liver with incidence and severity of any recorded findings.

Although the authors concluded that there were treatment-related effects on foetal and offspring body weight, there is no evidence from this study to suggest that glyphosate exposure has had any impact on foetal development or pup development postnatally. There was no effect on average birth weight of pups, the slight difference observed in the glyphosate-treated group should be attributed to the slightly larger mean litter size observed (14.4 pups compared to 10.8 in the control group). Although figure 1 shows a reduction in mean pup weight in the glyphosate and Roundup™ treated groups (male and females combined). Group mean body weight of pups by sex showed no statistical differences from control.

Given the small group size, the large inter animal variability observed, the lack of consistency between the same parameter across the sexes, timepoints or sampling matrices, and the deficiencies listed above, it not possible to clearly attribute any of the observed differences to glyphosate exposure. Therefore, the current study provides no evidence that glyphosate exposure causes lipid metabolism disruption in offspring following prenatal (in utero) exposure.
This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate used is not sufficiently characterised, only one dose level was tested, there was large inter animal variability observed and too few animals per dose level were analysed.

Edition No.: M-812273-01-1

Author	Zhang Jing-Wen; Xu Ding-Qi Feng Xi-Zeng
Source	Chemosphere, (2019 Dec) Vol. 237, pp. 124435. Electronic Publication Date: 23 Jul 2019 Journal code: 0320657. E-ISSN: 1879-1298. L-ISSN: 0045-6535.
Title	The toxic effects and possible mechanisms of glyphosate on mouse oocytes.
Publication Year	2019
Accession Number	2021419550 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
In vitro intracellular changes in Kunming mice oocytes were evaluated after being cultured in medium supplemented with 500 μM glyphosate. Findings included: decreased germinal vesicle breakdown, decreased first polar body extrusion, increased mRNA expression of anti-oxidant enzyme-related genes, abnormal spindle morphology, increased DNA double strand breaks, aggregated mitochondria, decreased mitochondrial membrane potential, increased protein expression of apoptosis factors, increased mRNA expression of apoptosis related genes and decreased autophagy-related genes.

No dose-response could be determined as only one concentration was tested, far in excess of that considered biologically relevant. Whilst some evaluations were conducted on oocytes harvested from a wider data set of 24 mice (protein expression levels of apoptosis factors by Western blot analysis), a number of the assessments were conducted on oocytes from just 12 mice (mRNA expression of oxidative stress-related, apoptosis-related and autophagy-related genes) or 6 mice (mitochondrial staining, measurement of mitochondrial membrane potential). This narrow source of oocytes limits the robustness of certain conclusions. Furthermore, there are insufficient details reported in the methods to establish whether mice were of the same age before oocyte harvesting or the purity of the glyphosate tested.
This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because of the poor characterisation of the glyphosate tested, no cytotoxicity testing, the lack of a positive control and insufficient dose-response characterisation at biologically relevant doses.

Edition No.: M-812245-01-1

Author	Johansson Hanna Katarina Lilith; Schwartz Camilla Lindgren; Nielsen Lene Norby; Boberg Julie; Vinggaard Anne Marie; Bahl Martin Iain Svingen Terje
Source	Reproductive toxicology (Elmsford, N.Y.), (20181200) Vol. 82, pp. 25-31. Electronic Publication Date: 27 Sep 2018 Journal code: 8803591. E-ISSN: 1873-1708. L-ISSN: 0890-6238.
Title	Exposure to a glyphosate-based herbicide formulation, but not glyphosate alone, has only minor effects on adult rat testis.
Publication Year	2018
Accession Number	2020341319 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The effects of glyphosate on intra-testicular testosterone levels, expression of Leydig cell-specific genes Cyp11a1, Cyp17a1, Insl3, Hsd3β1 and Star and expression of somatic marker gene Ar or germ cell marker gene Ddx4, expression of Leydig cell-specific steroidogenesis factors CYP11A1 and STAR, testicular histopathology and apoptosis were investigated in male rats treated orally at 0, 2.5 and 25 mg/kg bw/day for 2 weeks. No effects were found on either of the testicular parameters tested suggesting that glyphosate does not contribute to endocrine disrupting effects of the male reproductive system.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because only two dose levels were used to explore the dose-effect relationship for the endpoints assessed.

Edition No.: M-813319-01-1

Author	Panzacchi, Simona; Mandrioli, Daniele; Manservisi, Fabiana; Bua, Luciano; Falcioni, Laura; Spinaci, Marcella; Galeati, Giovanna; Dinelli, Giovanni; Miglio, Rossella; et al.
Source	Environmental Health (London, United Kingdom), (2018) Vol. 17, pp. 52/1-52/13. CODEN: EHAGAB. ISSN: 1476-069X.
Title	The Ramazzini Institute 13-week study on glyphosate-based herbicides at humanequivalent dose in Sprague Dawley rats: study design and first in-life endpoints evaluation
Publication Year	2018
Accession Number	2018:654578 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
In this study the general toxicity of glyphosate was compared against that of its reference formulation MON 52276 in pregnant rats and their progeny. Also the urinary excretion of glyphosate and AMPA was investigated. The test compounds were administered via the drinking water resulting in a daily dose of 1.75 mg glyphosate acid eq./ kg bw. The endpoints investigated were mortality, body weight, water and food consumption, and clinical signs in dams and offspring and litter data. There was no mortality and no statistically significant differences were observed among control, glyphosate, and MON 52276 groups in any of the endpoints investigated. Urinary concentrations of glyphosate and AMPA of rats treated with glyphosate at 1.75 mg/kg bw/day were comparable to those observed in rats treated with MON 52276 at 1.75 mg glyphosate acid eq. /kg bw/day. This indicates that the co-formulants in this glyphosate formulation have little influence on the oral bioavailability of glyphosate. In the treated rats, the majority of glyphosate was excreted in urine unchanged at levels of about 100-fold higher than that of AMPA and the mean urinary concentration of glyphosate increased with the duration of treatment.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because only one dose level for glyphosate and MON 52276 was considered, only 8 animals were used per dose and per sex and the method of analysis of glyphosate and AMPA in urine and its validation were not fully reported.

Edition No.: M-813273-01-1

Author	Perego Maria Chiara; Schutz Luis F; Spicer Leon J Caloni Francesca; Albonico Marco Cortinovis Cristina
Source	Journal of applied toxicology : JAT, (20170600) Vol. 37, No. 6, pp. 692-698. Electronic Publication Date: 5 Dec 2016 Journal code: 8109495. E-ISSN: 1099-1263. L-ISSN: 0260-437X.
Title	Evidence for direct effects of glyphosate on ovarian function: glyphosate influences steroidogenesis and proliferation of bovine granulosa but not theca cells in vitro.
Publication Year	2017
Accession Number	2017734568 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

In this *in vitro* study, glyphosate had minimal effects on granulosa cells (GC). In the presence of FSH only, glyphosate had no effect on GC cell viability or on progesterone or estradiol production. In the presence of FSH and IGF1, glyphosate reduced GC proliferation without a dose-response at 0.5 and 5 µg/mL but not at lower test concentrations (0.01 and 0.3 µg/mL) and did not affect progesterone production or CYP19A1 and CYP11A1 mRNA expression; estradiol production was reduced at 5 µg/mL only (not at lower test concentrations). Without FSH or IGF1, 1.7 µg/mL of glyphosate slightly increased GC proliferation in response to serum (≤11 %).

Glyphosate at 5 µg/mL had no effect on the theca cell (TC) proliferation or the production of progesterone or androstenedione.

Overall, with the exception of slight, non-dose-related alterations in GC proliferation under different test conditions, this study showed no effects of glyphosate on GC at physiologically relevant test concentrations. Glyphosate had no effect on TH.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate tested was not sufficiently characterised, no positive controls were used and the tests were conducted with only one or 2 test concentrations of glyphosate.

Edition No.: M-813261-01-1

Author	Dai Pengyuan; Hu Ping; Tang Juan; Li Yansen Li Chunmei
Source	Acta histochemica, (2016 Jun) Vol. 118, No. 5, pp. 519-26. Electronic Publication Date: 7 Jun 2016 Journal code: 0370320. E-ISSN: 1618-0372. L-ISSN: 0065-1281.
Title	Effect of glyphosate on reproductive organs in male rat.
Publication Year	2016
Accession Number	2017088191 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The potential toxicity of glyphosate to the male reproductive system of the rat has been investigated after oral treatment with glyphosate for 5 weeks at dose levels up to 500 mg/kg bw. The endpoints studied were body weight, food intake, daily weight gain, absolute and relative reproductive organ weight, serum hormone levels, oxidative stress parameters, testicular histopathology and expression of AR in testis. The effects found were a significant decrease in absolute (but not relative) weight of the seminal vesicle gland and coagulating gland and a decrease in sperm count at the highest dose tested.

This publication is considered relevant but reliable with restrictions because there are deviations from regulatory guidelines for reproductive toxicicity studies and the reproductive effects seen are not corroborated by the results from guideline studies at similar dose levels.

Edition No.: M-812364-01-1

Author	Forgacs Agnes L Ding Qi; Jaremba Rosemary G; Huhtaniemi Ilpo T; Rahman Nafis A; Zacharewski Timothy R
Source	Toxicological sciences : an official journal of the Society of Toxicology, (2012 Jun) Vol. 127, No. 2, pp. 391-402. Electronic Publication Date: 29 Mar 2012 Journal code: 9805461. E-ISSN: 1096-0929. L-ISSN: 1096-0929.
Title	BLTK1 murine Leydig cells: a novel steroidogenic model for evaluating the effects of reproductive and developmental toxicants.
Publication Year	2012
Accession Number	2012508575 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
In this study, recombinant human chorionic gonadotropin (rhCG) and forskolin (FSK) were used as positive controls for the induction of steroidogenesis, as measured by increases in progesterone, testosterone and 17β-estradiol levels in culture media. Murine BLTK1 Leydig cells were investigated as a novel model for evaluating the effects of chemicals on steroidogenesis. The results demonstrated that BLTK1 cells can be used to screen substances that alter intracellular cAMP, steroidogenic gene expression, and sex steroid levels. When tested in this system glyphosate was not found to induce testosterone production or alter rhCG induction of testosterone.

This publication is considered relevant for glyphosate risk assessment but reliable with restrictions because the test substance was not characterised and the results of only one concentration level were reported.

Edition No.: M-812301-01-1

Author	Ganesan Shanthi; McGuire Bailey C Keating Aileen F
Source	Reproductive toxicology (Elmsford, N.Y.), (2020 Jun 24) . Electronic Publication Date: 24 Jun 2020 Journal code: 8803591. E-ISSN: 1873-1708. L-ISSN: 0890-6238.
Title	Absence of glyphosate-induced effects on ovarian folliculogenesis and steroidogenesis.
Publication Year	2020
Accession Number	2022653178 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
In vivo study on post natal day 42, glyphosate administered to C57BL/6 J female mice at 0 or 2 mkd (10 mice/dose). Cyclicity, follicle number, circulating ovarian steroid hormone levels and ovarian intracellular signaling parameters were tested in adult female mice during 5 or 10 weeks. Glyphosate exposure for five or ten weeks did not affect the ovarian and endocrine endpoints examined.

The article is classified as reliable with restrictions for the following reasons: only 1 dose tested (no dose relationship can be evaluated), purity of glyphosate is not clear, method of analysis for analysis test media & no validation of the analytical method was described, no GLP status stated, no OECD guideline followed. Although no HCD were available in order to compare with the equivalent concurrent controls and test groups results, the results were negative and therefore did not require HCD to interpret or provide context to any findings.

Edition No.: M-812250-01-1

Author	Martinez Adriana Al-Ahmad Abraham Jacob
Source	Toxicology letters, (2019 Apr) Vol. 304, pp. 39-49. Electronic Publication Date: 31 Dec 2018 Journal code: 7709027. E-ISSN: 1879-3169. L-ISSN: 0378-4274.
Title	Effects of glyphosate and aminomethylphosphonic acid on an isogeneic model of the human blood-brain barrier.
Publication Year	2019
Accession Number	2020676778 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The effect of glyphosate, AMPA and glycine was investigated on the integrity of the blood-brain barrier *in vitro* using an induced pluripotent stem cell line differentiated into brain microvascular endothelial cells (BMEC) and neurons. The endpoints investigated were BMEC cell viability, fluorescein permeability in BMEC cell monolayers, tight junction complexes integrity, diffusion across the blood-brain barrier, modulation of glucose uptake in BMECs, barrier function of neurons co-cultured with BMECs, neurovascular coupling, differentiation of neuron progenitor cells and neurites density. The results of this study indicate that glyphosate or AMPA are unlikely to present toxicity towards the blood-brain barrier. Minimal effects on single parameters were observed with glyphosate or AMPA, but were comparable with effects of the amino acid glycine.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate used was not sufficiently characterized and no positive controls were used in any of the assays conducted.

Edition No.: M-812220-01-1

Author	Martinez Maria-Aranzazu; Ares Irma; Rodriguez Jose-Luis; Martinez Marta; Martinez-Larranaga Maria-Rosa; Anadon Arturo
Source	Environmental research, (20180200) Vol. 161, pp. 212-219. Electronic Publication Date: 20 Nov 2017 Journal code: 0147621. E-ISSN: 1096-0953. L-ISSN: 0013-9351.
Title	Neurotransmitter changes in rat brain regions following glyphosate exposure
Publication Year	2018
Accession Number	2019230663 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
Although the study concludes “loss of 5-HT, DA and NE levels in the CNS”, no historical controls are available to assess and compare the changes in the treatment-groups to ascertain if the effects are within background or if they are biologically relevant.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because there were no negative or positive historical control data to establish whether changes in the levels of neurotransmitters were biologically meaningful. No concurrent positive control was included to demonstrate assay viability. Also no analytical verification of dose levels are available.

Edition No.: M-812390-01-1

Author	Chorfa Areski Betemps Dominique; Morignat Eric; Lazizzera Corinne; Hogeveen Kevin; Andrieu Thibault; Baron Thierry
Source	Toxicological sciences : an official journal of the Society of Toxicology, (2013 Jun) Vol. 133, No. 2, pp. 289-97. Electronic Publication Date: 27 Mar 2013 Journal code: 9805461. E-ISSN: 1096-0929. L-ISSN: 1096-0929.
Title	Specific pesticide-dependent increases in α-synuclein levels in human neuroblastoma (SH-SY5Y) and melanoma (SK-MEL-2) cell lines
Publication Year	2013
Accession Number	2013502131 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The objective was to precisely assess changes in α-syn levels in human neuroblastoma (SH-SY5Y) and melanoma (SK-MEL-2) cell lines following acute exposure to glyphosate using Western blot and flow cytometry. The study was conducted using an *in vitro* test system. Glyphosate did not have any impact on the endpoints measured in this study. This is not a guideline study, nor did this study evaluate an endpoint used in risk assessment. Therefore, this study in not usable for quantitative human health risk assessment or hazard assessment.

This publication is considered reliable with restrictions (no positive control was included and only 2 test concentrations were used) but is not relevant for the risk assessment of glyphosate.

Edition No.: M-812275-01-1

Author	Hao Youwu; Xu Wenping; Zhang Yang; Yang Yun; Tao Liming Gao Jufang
Source	Journal of agricultural and food chemistry, (2019 Oct 16) Vol. 67, No. 41, pp. 11364-11372. Electronic Publication Date: 7 Oct 2019 Journal code: 0374755. E-ISSN: 1520-5118. L-ISSN: 0021-8561.
Title	Roundup-Induced AMPK/mTOR-Mediated Autophagy in Human A549 Cells.
Publication Year	2019
Accession Number	2021609437 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The effect of glyphosate, POEA and a herbicidal formulation containing POEA as a co-formulant on the AMPK/mTOR signaling pathway was studied in human alveolar carcinoma A549 cells in vitro. Only the results of exposure to glyphosate at 100 µg/mL are reported and discussed in this summary. The endpoints selected to study the effect of glyphosate on autophagy are inhibition of viability, monodansylcadaverine (MDC) staining to mark autophagic vacuoles, visualization of double-membrane autophagosomes by TEM, autophagic flux, colocalization of mitochondria and lysosomes, opening of the mitochondrial permeability transition pore (mPTP), expression of proteins involved in the AMPK/mTOR signaling pathway, and ATP content. No effect could be demonstrated of glyphosate on any of these endpoints indicating that glyphosate, in contrast to POEA and Roundup, does not contribute to the activation of the AMPK/mTOR signaling pathway and has thus no role in autophagy.

This publication is relevant for the risk assessment of glyphosate but reliable with restrictions because only one glyphosate concentration was tested and no positive controls were used.

Edition No.: M-812278-01-1

Author	Kwiatkowska Marta; Michalowicz Jaromir; Jarosiewicz Pawel; Pingot Daria; Sicinska Paulina; Jarosiewicz Monika Huras Bogumila; Zakrzewski Jerzy Bukowska Bozena
Source	Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association, (2020 Jan) Vol. 135, pp. 110888. Electronic Publication Date: 17 Oct 2019 Journal code: 8207483. E-ISSN: 1873-6351. L-ISSN: 0278
Title	Evaluation of apoptotic potential of glyphosate metabolites and impurities in human peripheral blood mononuclear cells (in vitro study).
Publication Year	2020
Accession Number	2021695873 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The study describes in-vitro investigations of glyphosate, its metabolites (AMPA and methylphosphonic acid) and impurities (PMIDA, N-methylglyphosate, hydroxymethylphosphonic acid, and bis-(phosphonomethyl)amine) on six intermediate endpoints of apoptosis (membrane permeability, cytosolic calcium concentration, mitochondrial transmembrane potential, caspase activity, chromatin condensation, and ROS quantitation by two methods) in human peripheral blood mononuclear cells. The reason for selection of this model is not stated but is possibly as potential target tissue for Non-Hodgkins Lymphoma. The methodologies used are frequently reported in literature but are not a standardized or validated method by GLP standards; there is no OECD guideline. Positive control results are not presented and it is unclear if positive controls were used for all assays; wording is sufficiently poor that it may be inferred that some positive controls were used, e.g. nigericin and valinomycin in the studies of mitochondrial transmembrane potential, campothecin in the caspase assays, although these may alternatively be reagents for the assay. It is unclear if assays were conducted in duplicate or triplicate (the stated term was “trice” which may be either twice or thrice), which may then also influence statistical evaluation. However, the methodology appears basically sound.

Apoptotic or pre-apoptotic activity was seen generally consistently across the assays. While glyphosate, its metabolites, and impurities were seen to increase apoptotic endpoints in these assays (0.5 mM and higher), clear effects occurred only at high concentrations.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because no proper cytotoxicity tests were performed, no positive controls were used and the concentration range at which most of the effects were observed is beyond the acceptable physiological range (> 1 mM). The concentration range at which the glyphosate impurities were tested is the same as that for glyphosate which is not a realistic approach for risk assessment of impurities.

Edition No.: M-813436-01-1

Author	Forsythe Steven D; Devarasetty Mahesh; Shupe Thomas; Bishop Colin; Atala Anthony; Soker Shay; Skardal Aleksander Atala Anthony; Soker Shay; Skardal Aleksander Soker Shay; Skardal Aleksander Soker Shay; Skardal Aleksander
Source	Frontiers in public health, (2018) Vol. 6, pp. 103. Electronic Publication Date: 16 Apr 2018 Journal code: 101616579. ISSN: 2296-2565. L-ISSN: 2296-2565. Report No.: PMC-PMC5932352.
Title	Environmental Toxin Screening Using Human-Derived 3D Bioengineered Liver and Cardiac Organoids.
Publication Year	2018
Accession Number	2019827431 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
In this study the toxicity of glyphosate for liver and cardiac organoids was investigated in the concentration range from 25 µM to 25 mM. The endpoints considered were cell viability, ATP activity and beating rate of the cardiomyocytes. Glyphosate was shown to reduce organoid integrity and viability at doses from 250 µM to 2.5 mM. The IC_{50} values based on ATP activity of liver and cardiac organoids were found to be 10.53 and 10.85 mM, respectively. When cardiac organoids were exposed to glyphosate at 0.25 mM a non-statistically significant effect was found on beating rate. Exposure to 2.5 mM for 2 days resulted in all organoids stopping beating.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate used was not characterized, no positive controls were used to validate the organoid test systems and the concentrations at which most of the effects have been observed are physiologically not feasible in *in vivo* experimental models.

Edition No.: M-812298-01-1

Author	Yahfoufi Zeina A Bai David; Khan Sana N; Chatzicharalampous Charalampos Kohan-Ghadr Hamid-Reza Morris Robert T Abu-Soud Husam M
Source	Toxicology, (2020 Jun) Vol. 439, pp. 152466. Electronic Publication Date: 19 Apr 2020 Journal code: 0361055. E-ISSN: 1879-3185. L-ISSN: 0300-483X.
Title	Glyphosate Induces Metaphase II Oocyte Deterioration and Embryo Damage by Zinc Depletion and Overproduction of Reactive Oxygen Species.
Publication Year	2020
Accession Number	2022377307 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The quality of metaphase II noncumulus oocytes and embryos from mice were investigated following glyphosate exposure at different concentrations (max 300 µM). The concentrations were in the range of those found in human blood following accidental acute oral exposure or suicidal attempts.

Results indicate that glyphosate provokes disruption of the microtubule organizing center and chromosomal disorganization at the mid-position of the spindle due to spindle disappearance, and defective chromosomal alignment as well as depletion of intracellular zinc bioavailability and enhancement of reactive oxygen species (ROS) accumulation in the mouse oocytes. In the embryos (not specified the source and the embryonal stage) zinc depletion and accumulation of ROS was also observed in a dose-related manner.

The article is classified as *reliable with restrictions* for the following reason: Not performed according to GLP or an OECD test guideline. No purity of the test substance stated. No information of the source and the embryonal stage of the embryos were provided. There were no concurrent positive control or substances known to deteriorates oocyte quality through disassembly of microtubule organizing centers (like peroxynitrite) or ROS accumulation (like hydrogen peroxide, and hypochlorous acid) or dimercapto-1-propanesulfonic acid (DMPS) for zinc depletion.

Edition No.: M-813433-01-1

Author	Mesnage, Robin (Reprint); Antoniou, Michael N.
Source	FRONTIERS IN PUBLIC HEALTH, (22 JAN 2018) Vol. 5. ISSN: 2296-2565.
Title	Ignoring Adjuvant Toxicity Falsifies the Safety Profile of Commercial Pesticides
Publication Year	2018
Accession Number	2018:1991741 SCISEARCH
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
This review article is presenting information on unverified effects of a small subset of co-formulants in some Glyphosate-based formulations, with an emphasis on POEA. This co-formulant is a surfactant banned in the EU glyphosate-based products.
Literature review section reaffirms low toxicity of the active ingredient compared with formulated products. No new data presented.

Edition No.: M-812511-01-1

Author	Ferramosca, Alessandra; Lorenzetti, Stefano; Di Giacomo, Mariangela; Murrieri, Francesco; Coppola, Lamberto; Zara, Vincenzo
Source	Reproductive Toxicology, (2021) Vol. 99, pp. 48-55. CODEN: REPTED. ISSN: 0890-6238.
Title	Herbicides glyphosate and glufosinate ammonium negatively affect human sperm mitochondria respiration efficiency.
Publication Year	2021
Accession Number	2020:713662 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

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.

Edition No.: M-813437-01-1

Author	Gigante Paolo; Berni Melissa; Bussolati Simona; Grasselli Francesca; Grolli Stefano; Ramoni Roberto Basini Giuseppina
Source	Animal reproduction science, (2018 Aug) Vol. 195, pp. 185-196. Electronic Publication Date: 24 May 2018 Journal code: 7807205. E-ISSN: 1873-2232. L-ISSN: 0378-4320.
Title	Glyphosate affects swine ovarian and adipose stromal cell functions.
Publication Year	2018
Accession Number	2019914845 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The effects of glyphosate on functional parameters of granulosa cells and adipose stromal cells from swine were investigated *in vitro*. In granulosa cells the effect of glyphosate was studied on cell proliferation, cell viability, steroid production, superoxide anion production, NO production and ferric reducing activity. In adipose stromal cells the effect of glyphosate was studied on cell viability, adipogenic differentiation, adipogenic marker genes (PPARγ and leptin), intracellular lipid accumulation and adipose cell count. Glyphosate was found to significantly decrease cell proliferation, cell viability, estrogen production and ferric reducing capacity and increase progesterone and NO production in granulosa cells when tested at concentrations ranging from 0.2 to 16 µg/mL. However, in none of the assays with granulosa cells a concentration-response relationship was established. Glyphosate treatment at 4 µg/mL significantly decreased ($p < 0.001$) the viability of proliferating adipose stromal cells after 48 and 72 hours. Differentiated cell counts showed a significant inhibition ($p < 0.05$) of the adipogenic process by glyphosate at 4 µg/mL. Since only one concentration of glyphosate was tested it was not possible to establish a concentration-response relationship. In this publication it is suggested that glyphosate interferes with the main functional parameters of the granulosa cell which could affect reproductive function. No effects on female reproductive function were reported in the rat in regulatory reproductive toxicology tests at doses beyond 2,000 mg/kg bw/day producing systemic glyphosate concentrations that are higher than those tested in this study.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate tested was not sufficiently characterized, no positive controls were included in the assays and only one dose level was used for the testing of adipose stromal cells.

Edition No.: M-812232-01-1

Author	Vanlaeys Alison Dubuisson Florine Seralini Gilles-Eric Travert Carine
Source	Toxicology in vitro : an international journal published in association with BIBRA, (2018 Oct) Vol. 52, pp. 14-22. Electronic Publication Date: 5 Jun 2018 Journal code: 8712158. E-ISSN: 1879-3177. L-ISSN: 0887-2333.
Title	Formulants of glyphosate-based herbicides have more deleterious impact than glyphosate on TM4 Sertoli cells.
Publication Year	2018
Accession Number	2019846850 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

In this study the effect of glyphosate on murine TM4 Sertoli cells was investigated *in vitro*. The endpoints were cytotoxicity, glutathione transferase activity and lipid accumulation. In contrast to the glyphosate-based formulations and co-formulants tested glyphosate was found to have no impact on cell viability after 24 hours of exposure at concentrations ranging from 10 ppm to 10,000 ppm. Glyphosate reduced succinate dehydrogenase to some extent over the entire concentration range from 10 (approx. 85 % of control) to 10,000 ppm (approx.75 % of control) with no dose-effect relationship and was found to have no impact on glutathione transferase activity. Exposure of TM4 cells to glyphosate for 24 hours at 2,500 or 5,000 ppm induces an increase in cytoplasmic lipid droplets. These concentrations are far beyond what is physiologically feasible *in vivo*.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the glyphosate used is not sufficiently characterized and no positive controls were used in any of the assays conducted.

Edition No.: M-812211-01-1

Author	Mesnage Robin; Phedonos Alexia; Biserni Martina Arno Matthew; Balu Sucharitha Corton J Christopher Ugarte Ricardo Antoniou Michael N
Source	Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association, (2017 Oct) Vol. 108, No. Pt A, pp. 30-42. Electronic Publication Date: 12 Jul 2017 Journal code: 8207483. E-ISSN: 1873-6351. L-I
Title	Evaluation of estrogen receptor alpha activation by glyphosate-based herbicide constituents.
Publication Year	2017
Accession Number	2018779530 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

The objective of this study was to evaluate the possible estrogenicity of glyphosate and glyphosate-based formulations and their adjuvants. The tests performed were the E-screen using different cell lines, the ERE-luciferase reporter gene assay, mmicroarray gene expression profiling and RNA-sequencing gene expression profiling. An increase in cell proliferation was observed in human breast cancer cells (MCF-7) at 10,000 µg/L and reached a maximum response at 1,000,000 µg/L. Similar but less pronounced results were observed with the T47D cell line. Glyphosate stimulated ERE-mediated transcription of the luciferase reporter gene starting at a concentration of 1,000 µg/L. The analysis of gene ontology confirms that genes having their expression altered by treatment of MCF-7 cells with glyphosate were involved in cell cycle regulation, stimulation by steroid hormones and cell death through apoptosis. ONIOM binding energy assessment strongly implies that the binding of glyphosate at the active site of the estrogen receptor is weak and unstable, suggesting that glyphosate is unlikely to bind to ERα.

This study has demonstrated that glyphosate activates ERα through a ligand-independent pathway only at high concentrations that are not encountered at typical exposure levels. This publication is considered relevant for glyphosate risk assessment and reliable without restrictions.

Edition No.: M-812177-01-1

Author	Thongprakaisang Siriporn Thiantanawat Apinya; Rangkadilok Nuchanart; Suriyo Tawit; Satayavivad Jutamaad
Source	Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association, (2013 Sep) Vol. 59, pp. 129-36. Electronic Publication Date: 10 Jun 2013 Journal code: 8207483. E-ISSN: 1873-6351. L-ISSN: 0278-
Title	Glyphosate induces human breast cancer cells growth via estrogen receptors.
Publication Year	2013
Accession Number	2013718176 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The objective of this study was to investigate the possible estrogenic effect of glyphosate and its mode of action. The endpoints explored were the cell proliferation of hormone-dependent and hormone-independent cell lines with and without an ER antagonist, ERE-transcription activity with and without an ER antagonist, and expression of ERs. Glyphosate was found to produce cell proliferation in a hormone-dependent cancer cell line but not in a hormone-independent cancer cell line in the absence of E2. In the presence of a potent ER antagonist the cell proliferation caused by glyphosate in a hormone-dependent cancer cell line was reduced. The interaction of glyphosate with the ER was confirmed by ERE activation with and without an ER antagonist. When cells were co-incubated with glyphosate and E2, glyphosate suppressed the E2-induced ERE activation suggesting that glyphosate behaves as an antagonist in the presence of an endogenous agonist. It was demonstrated that glyphosate alters the expression of both ERα and ERβ in human breast cancer cells.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the test results are not corroborated by in vivo regulatory ED toxicology studies such as the uterotrophic assay and the female pubertal assay (U.S. EPA Endocrine Disruptor Screening Program).

Edition No.: M-812299-01-1

Author	Gastiazoro M P Durando M; Milesi M M; Lorenz V; Varayoud J Vollmer G Zierau O
Source	Molecular and cellular endocrinology, (2020 Jun 15) Vol. 510, pp. 110841. Electronic Publication Date: 28 Apr 2020 Journal code: 7500844. E-ISSN: 1872-8057. L-ISSN: 0303-7207.
Title	Glyphosate induces epithelial mesenchymal transition-related changes in human endometrial Ishikawa cells via estrogen receptor pathway.
Publication Year	2020
Accession Number	2022422045 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
Ishikawa endometrial cancer cells were treated with glyphosate at 0.2 µM and 2 µM. Glyphosate caused cell migration, invasion ability and down regulated E-cadherin mRNA expression. 17ß-estradiol, which was included as a positive control caused similar epithelial mesenchymal transition related changes, while treatment with fulvestrant (estrogen receptor antagonist) reversed the effects caused by glyphosate. The findings suggest that glyphosate has the ability to trigger the estrogen receptor-dependant pathway.
The relevance to human health risk assessment of this unvalidated *in vitro* research model in an immortal adenocarcinoma cell line containing estrogen and progesterone receptors is not clear. The results contradict a number of higher tier studies conducted across a variety of test systems,
The article is classified as reliable with restrictions for the following reason : glyphosate was tested at two different concentrations only, no test guideline was used and no historical control data were provided in order to compare with the equivalent concurrent controls and test groups results. Further, the study was not performed according to GLP.

Edition No.: M-812289-01-1

Author	Xia Yongpeng; Lu Jingchun; Xie Qixin Yang Xiaobo Ye Anfang Sun Wenjun
Source	Environmental pollution (Barking, Essex : 1987), (2020 May) Vol. 260, pp. 113949. Electronic Publication Date: 14 Jan 2020 Journal code: 8804476. E-ISSN: 1873-6424. L-ISSN: 0269-7491.
Title	The endoplasmic reticulum stress and related signal pathway mediated the glyphosate-induced testosterone synthesis inhibition in TM3 cells.
Publication Year	2020
Accession Number	2022031709 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
In vitro study on the effects of glyphosate on testosterone secretion and the role of endoplasmic reticulum stress in the process were investigated in TM3 cells. Results showed that exposure to glyphosate at concentrations below 200 mg/L had no effect on cell viability, while glyphosate at concentrations above 0.5 mg/L could inhibit the testosterone secretion in TM3 cells. Treatment of TM3 cells with glyphosate at 5 mg/L not only reduced the protein levels of testosterone synthase StAR and CYP17A1 but also inhibited testosterone secretion.

The article is classified as reliable with restrictions for the following reason: not enough information on the tested material (purity) was provided, no positive controls were used, and no statistical methods were described. Furthermore, no OECD guidelines were followed, no GLP status was stated, and no historical control data (HCD) were provided to compare the relevance of data. In addition, key literature in disagreement with the authors' findings appear to have been disregarded, suggesting bias within the research and the following publications: Hecker (2011), OECD validation of the H295R steroidogenesis assay with glyphosate; Levine (2007), demonstrating a lack of effect of glyphosate on the StAR protein; US EPA (2015), glyphosate EDSP weight of evidence evaluation; and EFSA (2017), peer review of glyphosate potential endocrine-disrupting properties.

Hecker M et al (2011), The OECD validation program of the H295R steroidogenesis assay: Phase 3. Final inter-laboratory validation study, Environmental Science and Pollution Research 18(3):503-15

Levine S. L. Et al. (2007), Disrupting mitochondrial function with surfactants inhibits
MA-10 Leydig cell steroidogenesis, Cell Biol Toxicol (2007) 23:385-400

US EPA (2015), EDSP Weight of Evidence Conclusions on the Tier 1 Screening Assays for the List 1 Chemicals - EDSP: WEIGHT OF EVIDENCE ANALYSIS OF POTENTIAL INTERACTION WITH THE ESTROGEN, ANDROGEN OR THYROID PATHWAYS - CHEMICAL: GLYPHOSATE

EFSA (2017): Peer review of the pesticide risk assessment of the potential endocrine disrupting properties of glyphosate, Question number: EFSA-Q-2016-00663

Edition No.: M-813582-01-1

Author	Ferreira Catarina; Pereira Andre M P T; Silva Liliana J G; Lino Celeste; Pena Angelina Duarte Sofia C Costa Eduardo Almeida Anabela
Source	Environmental research, (2021 May 07) Vol. 198, pp. 111294. Electronic Publication Date: 7 May 2021 Journal code: 0147621. E-ISSN: 1096-0953. L-ISSN: 0013-9351.
Title	Urine biomonitoring of glyphosate in children: Exposure and risk assessment.
Publication Year	2021
Accession Number	2024026141 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
This is a small biomonitoring study with limited urine sample collection for each participant. The sampling strategy was not described, but the focus on recruiting participants from municipalities that subscribed to the "Municipalities without Glyphosate" campaign means that the results cannot be taken to be representative of the population of Portuguese children ages 2 to 13. Also, since 82% of the participants came from one region (Coimbra), and other regions had as few as 1 or 2 participants, it seems almost certain that the sampling strategy was a convenience sample. The results should be interpreted accordingly.

The authors concluded that age, living near agricultural areas, consumption of home-produced foods, and having herbicides applied in the backyard were predictors of urinary glyphosate concentrations. The actual differences in urinary concentrations across the categories of these factors were slight and none of the differences were statistically significant. Further, the analysis for each potential predictive factor was univariate and did not control for the other potential predictors. Thus, the authors' evaluation of potential predictors of urinary concentration is relatively uninformative.

The authors estimated that the study participants had glyphosate oral ingestion ranging from 1% to 5.6% of the glyphosate ADI (0.5 mg/kg bw). These estimates were based on assuming 1% oral glyphosate absorption as estimated by Zoller et al. (2020). One percent absorption is 20-fold lower than the absorption factor used previously in the literature (e.g., Niemann et al. 2015). However, the Zoller et al. (2020) study was a well-controlled human study and the 1% absorption is potentially representative for low oral exposures to glyphosate. Zoller et al. (2020) noted, with respect to the 1% absorption factor, that human glyphosate intake estimated from urinary concentrations could be approximately 20 times greater than previously estimated and that would be counterbalanced by human systemic availability being 20 times

lower than previously assumed. Assuming 1% absorption is valid, the estimated intakes in this study are 18-fold to 100-fold less than the ADI.

To conclude, the study by Ferreira and colleagues (2021) has several important limitations. The study participants are unlikely to be representative of children in Portugal. Urine collection per participant was limited to one spot sample, which requires assumptions about the daily volume of urine for each participant and about whether the single sample is representative of that participant's steady state throughout the year. The statistical analysis was superficial with respect to factors that might predict oral intake. Setting aside these limitations and taking the % ADI results at face value, the highest value seen in this study is a small percentage of the ADI.

References

Niemann L, Sieke C, Pfeil R, Solecki R. A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers. Journal für Verbraucherschutz und Lebensmittelsicherheit 2015;10(1):3-12.

Zoller O, Rhyn P, Zarn JA, Dudler V. Urine glyphosate level as a quantitative biomarker of oral exposure. International Journal of Hygiene and Environmental Health 228 (2020) 113526.

Edition No.: M-813371-01-1

Author	Shrestha, Srishti; Parks, Christine G.; Umbach, David M.; Richards-Barber, Marie; Hofmann, Jonathan N.; Chen, Honglei; Blair, Aaron; Beane Freeman, Laura E.; Sandler, Dale P.
Source	Environmental Research, (2020) Vol. 191, pp. 110186. CODEN: ENVRAL. ISSN: 0013-9351.
Title	Pesticide use and incident Parkinson's disease in a cohort of farmers and their spouses.
Publication Year	2020
Accession Number	2020:556332 TOXCENTER
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
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.

Edition No.: M-813448-01-1

Author	Werder, Emily J.; Sandler, Dale P. (correspondence) Werder, Emily J.; Engel, Lawrence S. Satagopan, Jaya Blair, Aaron; Koutros, Stella; Lerro, Catherine C.; Alavanja, Michael C.; Beane Freeman, Laura E. Sandler, Dale P. (correspondence)
Source	Environmental Epidemiology, (2020) Vol. 4, No. 3. arn. e097. Refs: 49 E-ISSN: 2474-7882
Title	Herbicide, fumigant, and fungicide use and breast cancer risk among farmers' wives.
Publication Year	2020
Accession Number	20200539871 EMBASE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

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.

Edition No.: M-806137-01-1

Author	Andreotti, Gabriella (Correspondence); Freeman, Laura E. Beane; Coble, Joseph; Silverman, Debra T.; Alavanja, Michael C. R.
Source	International Journal of Cancer, (15 May 2009) Vol. 124, No. 10, pp. 2495-2500. Refs: 25 ISSN: 0020-7136; E-ISSN: 1097-0215 CODEN: IJCNAW
Title	Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort.
Publication Year	2009
Accession Number	2009338239
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This was a case-control study conducted in the Agricultural Health Study cohort in Iowa and North Carolina, USA. The study population comprised licensed private and commercial pesticide applicators and their spouses. The health outcome of interest was incident pancreatic cancer, and was captured from population-based state cancer registries; it was defined as codes C25.0 – C25.9 in the International Classification of Diseases 10th Revision (ICD-10). The exposure of interest was glyphosate use, and was captured by self-administered questionnaire; exposure status was classified in two different ways: ever vs. never exposure, and number of exposure days. Data for 93 pancreatic cancer cases and 82,503 controls were analyzed using logistic regression. The reported an odds ratio (OR) and 95% confidence interval (CI) of 1.1 (0.6, 1.7) for participants who self-reported to have ever used glyphosate compared to those who self-reported to have never used it. Age group, cigarette smoking, diabetes, and applicator type were adjusted for in this analysis. The reported OR and 95% CI for participants with ≤184 days of exposure compared to those who self-reported to have never used it was 1.9 (0.9, 3.8). The OR and 95% CI for participants with ≥185 days compared to those who self-reported to have never used it was 1.2 (0.6, 2.6). The reported value for p-trend was 0.85. Age group, cigarette smoking, and diabetes were adjusted for in this analysis. These results suggest that there is not a statistically significant difference in pancreatic cancer incidence among exposure groups at the 0.05 significance level. This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because exposure classification was based on self-reported glyphosate use, an indirect method by which to estimate exposure status of study participants. No biological evidence is provided to support exposure classification of study participants. Misclassification of exposure is possible in this study.

Edition No.: M-806119-01-1

Author	Weselak, Mandy; Arbuckle, Tye E.; Wigle, Donald T.; Krewski, Daniel
Source	Environmental Research, (JAN 2007) Vol. 103, No. 1, pp. 79-86.
Title	In utero pesticide exposure and childhood morbidity.
Publication Year	2007
Accession Number	2007:138575
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This was a retrospective cohort study conducted in Canada as part of the Ontario Farm Family Health Study (OFFHS). The study population comprised children of married couples, or couples living as married, who lived year-round on a farm with reported agricultural product sales of at least $50,000 in 1986. Wives were aged 44 years or younger. The health outcomes of interest were chronic bronchitis or cough, asthma, hayfever or allergies in children, and was captured via questionnaire; it was defined as self-reported physician diagnosis. The exposure of interest was reported farm use of glyphosate during pregnancy, and was self-reported via questionnaire. Data from 3,405 children were analyzed using logistic regression and generalized estimating equations. The reported adjusted ORs and 95% CIs for children with reported glyphosate use during pregnancy compared to those without was 0.71 (0.21, 2.35) for persistent cough or bronchitis, 0.82 (0.35, 1.90) for asthma, and 0.98 (0.46, 2.10) for hayfever or allergies. Analyses for persistent cough or bronchitis were adjusted for child's age at time of questionnaire, father's age at conception, income, breast feeding, and mother's age at conception. Analyses for asthma were adjusted for child's age at time of questionnaire, and father's education level. Analyses for hayfever or allergies were adjusted for child's age at time of questionnaire, father's age at conception, mother's age at conception, and father's education level. These results suggest that there is not a statistically significant difference in odds of persistent cough or bronchitis, asthma, or hayfever or allergies among exposure groups at the 0.05 significance level. This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because exposure classification was based on self-reported glyphosate use, an indirect method by which to estimate exposure status of study participants. No biological evidence is provided to support exposure classification of study participants. Additionally, outcome classification was based on self-report of physician diagnosis. Misclassification of either exposure, outcome, or both is possible in this study.

Edition No.: M-805992-01-1

Author	Eriksson Mikael; Hardell Lennart; Carlberg Michael; Akerman Mans
Source	International journal of cancer, (2008 Oct 01) Vol. 123, No. 7, pp. 1657-63.
Title	Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis.
Publication Year	2008
Accession Number	2008493234
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This was a case control study conducted in Sweden. The study population comprised consecutive patients aged 18-74 years with newly diagnosed Non-Hodgkin lymphoma (NHL), and population controls selected from the same health service region. The health outcome of interest was NHL and its subtypes; diagnosis was confirmed by a pathologist. The exposure of interest was self-reported exposure or non-exposure to glyphosate, and number of days exposed; it was self-reported via questionnaire and, in some cases, interview. Data from 910 NHL cases and 1,016 controls were analyzed using logistic regression. The reported OR and 95% CI for participants exposed to glyphosate compared to those not exposed was 2.02 (1.10, 3.71). The reported OR and 95% CI for participants with 10 or fewer exposure days compared to those not exposed was 1.69 (0.70, 4.07), and the reported OR and 95% CI for participants with more than 10 exposure days compared to those not exposed was 2.36 (1.04, 5.37). When comparing participants with self-reported exposure and those with self-reported non-exposure reported ORs and 95% CIs were 1.87 (0.998, 3.51) for B-cell lymphomas, 3.35 (1.42, 7.89) for lymphocytic lymphoma/B-CLL (SLL/CLL), 1.89 (0.62, 5.79) for follicular, grade I-III (FL), 1.22 (0.44, 3.35) for diffuse large B-cell lymphoma (DLBCL), 1.63 (0.53, 4.96) for other specified B-cell lymphoma, 1.47 (0.33, 6.61) for unspecified B-cell lymphoma, 2.29 (0.51, 10.4) for T-cell lymphomas, and 5.63 (1.44, 22.0) for unspecified non-Hodgkin lymphoma. Controls were frequency matched on 10 year age and sex; analyses were adjusted for year of diagnosis for cases and of enrollment in controls. These results suggest that there is a statistically significant difference in odds of glyphosate exposure between NHL and non-NHL cases at the 0.05 significance level. Results were statistically significant for participants with more than 10 exposure days, but not for those with 10 or fewer compared to those who were non-exposed. This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because exposure classification was based on self-reported glyphosate use, an indirect method by which to estimate exposure status of study participants. No biological evidence is provided to support exposure classification of study participants. Misclassification of exposure is possible in this study.

Edition No.: M-806446-01-1

Author	Lee, Won Jin; Sandler, Dale P.; Blair, Aaron; Samanic, Claudine; Cross, Amanda J.; Alavanja, Michael C. R.
Source	Int. J. Cancer, Volume 121, Issue 2, Page 339-346, Publication Year 2007
Title	Pesticide use and colorectal cancer risk in the Agricultural Health Study.
Publication Year	2007
Accession Number	2007:677654
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This was a case-control study conducted in the Agricultural Health Study cohort in Iowa and North Carolina, USA. The study population comprised certified pesticide applicators and their spouses. The health outcome of interest was incident colorectal cancer, and was captured from a cancer registry. The exposure of interest was self-reported ever or never exposure to glyphosate, and was captured by questionnaire. Data for 305 colorectal cancer cases, and 56,508 non-cases were analyzed using unconditional multivariate logistic regression. The reported ORs and 95% CIs were 1.2 (0.9, 1.6) for colorectal cancer, 1.0 (0.7, 1.5) for colon cancer, and 1.6 (0.9, 2.9) for rectum cancer. Analyses were adjusted for age, state of residence, smoking history, and total pesticide application days for any pesticide. These results suggest that there is no statistically significant difference between odds of glyphosate exposure between cases and non-cases of colorectal cancer, colon cancer, or rectum cancer at the 0.05 significance level. This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because exposure classification was based on self-reported glyphosate use, an indirect method by which to estimate exposure status of study participants. No biological evidence is provided to support exposure classification of study participants. Misclassification of exposure is possible in this study.

Edition No.: M-520073-01-1

Author	Hoppin, Jane A.; Umbach, David M.; London, Stephanie J.; Lynch, Charles F.; Alavanja, Michael C. R.; Sandler, Dale P.
Source	Ann. N. Y. Acad. Sci., Volume 1076, Issue Living in a Chemical World, Page 343-354, Publication Year 2006
Title	Pesticides and adult respiratory outcomes in the agricultural health study.
Publication Year	2006
Accession Number	2006:1231821
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This was a cross-sectional study conducted in the Agricultural Health Study cohort in Iowa and North Carolina, USA. The study population comprised private and commercial pesticide applicators and their spouses. The health outcome of interest was self-reported wheeze, and was captured by self-administered questionnaire; it was defined as having had at least one reported episode of wheezing or whistling in the chest in the past 12 months. The exposure of interest was self-reported glyphosate use in the year before enrollment, and was captured by self-administered questionnaire. Data from 17,920 farmers and 2,255 commercial applicators were analyzed using logistic regression. Reported ORs and 95% CIs comparing participants with self-reported glyphosate use and those without were 1.05 (0.94, 1.17) among farmers, and 1.14 (0.83, 1.57) among commercial applicators. Analyses were adjusted for age, BMI, smoking, asthma/atopy, and previous use of pesticide. Analyses among commercial applicators also adjusted for chlorimuron-ethyl, and those among farmers also adjusted for state. These results suggest that there is no statistically significant difference in odds of self-reported glyphosate use and wheeze among either farmers or commercial applicators at the 0.05 significance level. This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because exposure classification was based on self-reported glyphosate use, an indirect method by which to estimate exposure status of study participants. No biological evidence is provided to support exposure classification of study participants. Additionally, outcome classification was based on self-report. Misclassification of either exposure, outcome, or both is possible in this study.

Edition No.: M-812240-01-1

Author	Connolly Alison Basinas Ioannis; Galea Karen S Jones Kate; Kenny Laura McGowan Padraic Coggins Marie A
Source	International journal of hygiene and environmental health, (20180800) Vol. 221, No. 7, pp. 1012-1022. Electronic Publication Date: 8 Jul 2018 Journal code: 100898843. E-ISSN: 1618-131X. L-ISSN: 1438-4639.
Title	Characterising glyphosate exposures among amenity horticulturists using multiple spot urine samples.
Publication Year	2018
Accession Number	2020151865 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

In this study the exposure of amenity horticulturalists to glyphosate was assessed. Three similar exposure groups (SEGs) were considered for the application of various glyphosate based herbicides: one using a manual knapsack, one using a pressurized handheld lance and one using a controlled droplet applicator. Urine samples were taken pre-task, post-task and the morning after the task and analysed for glyphosate using and LC-MS/MS method with an LOQ of 0.5 µg/L. Glyphosate concentrations were found to be less than the LOQ in 27% of the urinary samples, of which 38% were pre-task samples and 38% were following morning void samples. Two of the 29 work tasks had peak samples with urinary glyphosate concentrations below the LOQ, both belonging to the manual knapsack SEG. The geometric means of the glyphosate concentrations measured in urine samples of the combined glyphosate SEGs were 0.68 µg/L for pre-task samples, 1.17 µg/L for post-task samples and 0.83 µg/L for following morning void samples. 100% of the workers wore gloves, 90% a Tyvec suit and 97% RPE.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because more detail could have been provided on the validation of the analytical method. Also the number of participants per exposure scenario was rather limited.

Edition No.: M-812246-01-1

Author	Connolly Alison Jones Kate; Kenny Laura Basinas Ioannis; Galea Karen S McGowan Padraic Coggins Marie A
Source	International journal of hygiene and environmental health, (2019 Mar) Vol. 222, No. 2, pp. 205-210. Electronic Publication Date: 5 Oct 2018 Journal code: 100898843. E-ISSN: 1618-131X. L-ISSN: 1438-4639.
Title	Exploring the half-life of glyphosate in human urine samples.
Publication Year	2019
Accession Number	2020366297 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

Analytical data for glyphosate obtained from spot urine samples collected during a glyphosate exposure study (Connolly et al., International journal of Hygiene and Environmental Health (2018), Vol. 221, 1012-1022) were used to estimate the human biological half-life of glyphosate. To that end only work tasks with at least two spot urine samples collected after the peak exposure were included for excretion profile analysis. Glyphosate concentrations were log transformed and the slope of the glyphosate urine concentration by the time duration (time passed from the start time) was calculated for each task. When the results were restricted to sample sets which showed very strong relationships ($R^2 > 0.90$), the estimated half-life average (range) was 4.5 (1.5 - 7) hours and 7.5 (4.75 - 9.25) hours for unadjusted and creatinine corrected values, respectively. UER calculated samples showed moderate to strong relationship ($R^2 = 0.60–0.95$), with an estimated half-life average (range) of 7.25 (3 and 9.50) hours. This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions in view of the limitations of the study such as the lack of standardization (pesticide products used, quantity of pesticides applied per task, different application methods and different sampling times). The small sample size prevented the use of more elaborate statistical tests to identify differences due to sex or age. The pharmacokinetic analysis revealed first order kinetics but due to the collection of urine samples over a limited period of time (19-26 hours) multi-phasic kinetics may not have been identified.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions in view of the limitations of the study such as the lack of standardization (pesticide products used, quantity of pesticides applied per task, different application methods and different sampling times). The small sample size prevented the use of more elaborate statistical tests to identify differences due to sex or age. The pharmacokinetic analysis revealed first order kinetics but due to the collection of urine samples over a limited period of time (19-26 hours) multi-phasic kinetics may not have been identified.

Edition No.: M-813308-01-1

Author	Connolly Alison Jones Kate; Kenny Laura Galea Karen S; Basinas Ioannis McGowan Padraic Coggins Marie
Source	International journal of hygiene and environmental health, (20170800) Vol. 220, No. 6, pp. 1064-1073. Electronic Publication Date: 27 Jun 2017 Journal code: 100898843. E-ISSN: 1618-131X. L-ISSN: 1438-4639.
Title	Exposure assessment using human biomonitoring for glyphosate and fluroxypyr users in amenity horticulture.
Publication Year	2017
Accession Number	2018736404 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
Biological monitoring has previously been used in studies evaluating occupational exposures to pesticides in both the agricultural and horticultural sectors. The aim of this study was to characterise the occupational exposures in amenity horticultural workers using a biomonitoring method for glyphosate in urine. The geometric mean of the urinary glyphosate concentrations in the post-work samples of all exposure groups combined was found to be 0.66 µg/L. When the relationship between urinary concentrations of glyphosate and systemic dose as established by Acquavella et al. (Acquavella et al. (2004) Environmental Health Perspectives, 112(3), 321-326) is taken into consideration, the daily systemic dose for the workers in this study is estimated to be 0.000021 mg/kg bw/day. The corresponding daily oral external dose is about 0.0001 mg/kg bw/day when an oral bioavailability of 20% is taken into account. This is 5,000 times lower than the ADI of 0.5 mg/kg bw/day.

This publication is considered relevant for glyphosate risk assessment and reliable without restrictions because it complies with all the reliability criteria of an exposure study.

Edition No.: M-812231-01-1

Author	Connolly Alison Leahy Michelle; Coggins Marie A Jones Kate; Kenny Laura
Source	Environmental research, (20180800) Vol. 165, pp. 235-236. Electronic Publication Date: 3 May 2018 Journal code: 0147621. E-ISSN: 1096-0953. L-ISSN: 0013-9351.
Title	Glyphosate in Irish adults - A pilot study in 2017.
Publication Year	2018
Accession Number	2019800985 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
This study is newly submitted for purpose of review. A biomonitoring survey involving the collection and analysis of 20 ml spot urine samples from 50 Irish adults on non-occupational setting was conducted. The LC-MC/MS analyses of urinary samples revealed that 10 out of 50 samples analysed (i.e. 20%) contained detectable levels of glyphosate (0.80 – 1.35 µg/L). The low proportion of detectable glyphosate levels could be due to lower localised use of pesticides, having a small sample size or the higher analytical detection limit used in this study (0.5 µg/L).

This publication is considered relevant for the risk assessment of glyphosate and reliable without restrictions because it complies with the quality criteria of a good exposure study.

Edition No.: M-813459-01-1

Author	Connolly Alison; Coggins Marie A Galea Karen S; Basinas Ioannis Jones Kate; Kenny Laura McGowan Padraic
Source	Annals of work exposures and health, (2019 Feb 16) Vol. 63, No. 2, pp. 133-147. Journal code: 101698454. E-ISSN: 2398-7316. L-ISSN: 2398-7308.
Title	Evaluating Glyphosate Exposure Routes and Their Contribution to Total Body Burden: A Study Among Amenity Horticulturalists.
Publication Year	2019
Accession Number	2020679597 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
This study is newly submitted for purpose of review. The total uptake of glyphosate was assessed in parallel with dermal and inadvertent exposure routes, using urine, wipes and glove samples collected from 20 workers across 29 work tasks. The average hand surface area measurements were assigned according to published US EPA guidance. Geometric mean (GM) glyphosate concentrations of 0.01, 0.04 and 0.05 µg/cm2 were obtained on wipes from the workers' perioral region and left and right hands, respectively. For disposable and reusable gloves, respectively, GM glyphosate concentrations of 0.43 and 7.99 µg/cm2 were detected. The combined hand and perioral region glyphosate concentrations explained 40% of the variance in the urinary (µg/L) biomonitoring data. Data show the dermal exposure is the prominent route of exposure in comparison to inadvertent ingestion, but inadvertent ingestion may contribute to overall body burden. The study also identified potential exposure to non-pesticide users in the workplace and para-occupational exposures.

This publication is considered relevant for the risk assessment of glyphosate and reliable without restrictions because it complies with the quality criteria of a good exposure study.

Edition No.: M-813271-01-1

Author	Conrad Andre Schroter-Kermani Christa; Ruther Maria; Pieper Silvia; Kolossa-Gehring Marike Hoppe Hans-Wolfgang
Source	International journal of hygiene and environmental health, (2017 Jan) Vol. 220, No. 1, pp. 8-16. Electronic Publication Date: 29 Sep 2016 Journal code: 100898843. E-ISSN: 1618-131X. L-ISSN: 1438-4639.
Title	Glyphosate in German adults - Time trend (2001 to 2015) of human exposure to a widely used herbicide
Publication Year	2017
Accession Number	2017655168 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
The internal exposure levels of glyphosate and its main metabolite AMPA were analysed using the general German population urinary samples collected during a period covering 2001 – 2015 with similar sample sizes and sex distributions. Retrospective GC-MS-MS analyses revealed that 31.8% of analysed samples contained detectable level of glyphosate. For AMPA this was the case for 40.1% samples analysed. A peak of detectable glyphosate level was observed in 2012 (57.5%) and 2013 (56.4%), followed by a decrease in 2014 (32.5%) and 2015 (40.0%), which may be due to changes in glyphosate application in agricultural practice. Urinary glyphosate levels tended to be higher in males. Overall, the urinary level of AMPA showed a similar trend as glyphosate, with a statistically significantly correlation.

This publication is considered relevant for the risk assessment of glyphosate and reliable without restrictions because it complies with the quality criteria of a good monitoring study.

Edition No.: M-812204-01-1

Author	Kongtip Pornpimol; Nankongnab Noppanun; Phupancharoensuk Ratanavadee; Palarach Chonlada Sujirarat Dusit Sangprasert Supha Sermsuk Malasod Sawattrakool Namthip Woskie Susan Renee
Source	Journal of agromedicine, (2017) Vol. 22, No. 3, pp. 282-289. Journal code: 9421530. E-ISSN: 1545-0813. L-ISSN: 1059-924X.
Title	Glyphosate and Paraquat in Maternal and Fetal Serums in Thai Women.
Publication Year	2017
Accession Number	2018491282 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
This study suggests that agricultural activities increase maternal serum levels of glyphosate, even in samples taken on the day of birth. Living near farmland where pesticides are sprayed can also significantly increase the risk of serum levels >LOD at birth. Limitations of this study include a small sample size (N=82) and large percentages of maternal samples cord serum that were at or below the LOD for glyphosate (46.3% and 50.7%, respectively).

This publication is considered relevant to the risk assessment of glyphosate but reliable with restrictions because the analytical method used for glyphosate could have been described in more detail.

Edition No.: M-812183-01-1

Author	McGuire Michelle K McGuire Mark A Price William J; Shafii Bahman Carrothers Janae M; Lackey Kimberly A Goldstein Daniel A; Jensen Pamela K; Vicini John L
Source	The American journal of clinical nutrition, (2016 May) Vol. 103, No. 5, pp. 1285-90. Electronic Publication Date: 30 Mar 2016 Journal code: 0376027. E-ISSN: 1938-3207. L-ISSN: 0002-9165.
Title	Glyphosate and aminomethylphosphonic acid are not detectable in human milk.
Publication Year	2016
Accession Number	2016853271 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
In this study breast milk and urine samples from lactating women were analysed for glyphosate and AMPA. The results provide evidence that the concentrations of glyphosate and AMPA in milk produced by healthy women are below the detection limits of available validated analytical assays. In urine, glyphosate and AMPA were detectable in many samples, but the concentrations were very low and well below the values reported in other healthy adult populations.

This publication is considered relevant for the risk assessment of glyphosate and reliable without restrictions because it complies with all the reliability criteria of an exposure study.

Edition No.: M-813337-01-1

Author	Sierra-Diaz, Erick; de Jesus Celis-De la Rosa, Alfredo; Lozano-Kasten, Felipe; Trasande, Leonardo; Peregrina-Lucano, Alejandro Aaron; Sandoval-Pinto, Elena; Gonzalez-Chavez, Humberto
Source	International Journal of Environmental Research and Public Health, (2019) Vol. 16, No. 4, pp. 562. CODEN: IJERGQ. ISSN: 1660-4601.
Title	Urinary pesticide levels in children and adolescents residing in two agricultural communities in Mexico
Publication Year	2019
Accession Number	2019:355768 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

In a comparative cross-sectional study using the urine of children living in two agricultural communities with very similar characteristics in Mexico (a total of 281 children participated in the study), glyphosate was detected in more than 70% of the cases in both communities. The mean urinary levels of glyphosate were 0.363 ± 0.3210 ng/mL in Agua Caliente and 0.606 ± 0.5435 ng/mL in Ahuacapán.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because no validation data were presented for the analytical method employed.

Edition No.: M-812155-01-1

Author	Steinborn Angelika; Alder Lutz; Michalski Britta Zomer Paul; Mol Hans G J Bendig Paul; Martinez Sandra Aleson; Class Thomas J Pinheiro Nathalie Costa
Source	Journal of agricultural and food chemistry, (2016 Feb 17) Vol. 64, No. 6, pp. 1414-21. Electronic Publication Date: 8 Feb 2016 Journal code: 0374755. E-ISSN: 1520-5118. L-ISSN: 0021-8561.
Title	Determination of Glyphosate Levels in Breast Milk Samples from Germany by LC-MS/MS and GC-MS/MS.
Publication Year	2016
Accession Number	2016639110 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

Two analytical methods were developed for the determination of glyphosate in human breast milk. In the first method fat was removed by centrifugation and the proteins by ultra-filtration using a molecular weight cutoff filter of 30 kDa. The final extract was then analysed by LC-MS/MS. In the second method the milk sample was acidified with acetic acid, centrifuged and the supernatant extracted with dichloromethane. The aqueous phase was filtered and cleaned-up using a cation exchange resin. The final extract was then analysed by GC-MS/MS after derivatization with heptafluoro-1-butanol and trifluoroacetic acid anhydride. $^{13}C_2{}^{15}N$ glyphosate was used as the internal standard in both methods. Both analytical methods were validated according to the EU guidance document on analytical quality control and validation procedures for pesticide residues in food and feed (SANCO/12571/2013) and were found suitable for the determination of glyphosate in human breast milk with LOQ of 1 ng/mL and LOD of 0.5 ng/mL. In August and September 2015, 114 breast milk samples were collected from German women and were analysed for glyphosate. In none of the samples analysed glyphosate concentrations were found at or beyond the LOD.

This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the breast milk samples analysed were collected on a voluntary basis and there were no restrictions for participating in the monitoring program. As a consequence the samples cannot be considered representative of the German population. Both analytical methods developed were validated in accordance with the EU guidance on the procedures for the analysis of pesticide residues in food and feed.

Edition No.: M-812280-01-1

Author	Trasande Leonardo Aldana Sandra India Trachtman Howard Kannan Kurunthachalam; Karthikraj Rajendiran Morrison Deborah; Messito Mary Jo; Gross Rachel S Christakis Dimitri A; Whitlock Kathryn Sathyanarayana Sheela
Source	Environmental pollution (Barking, Essex : 1987), (2020 Jan) Vol. 256, pp. 113334. Electronic Publication Date: 23 Oct 2019 Journal code: 8804476. E-ISSN: 1873-6424. L-ISSN: 0269-7491.
Title	Glyphosate exposures and kidney injury biomarkers in infants and young children.
Publication Year	2020
Accession Number	2021742762 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
This study evaluated three cohorts across different phases of child development and measured urinary levels of glyphosate. They evaluated associations of glyphosate with three biomarkers of kidney injury: ACR, NGAL, and KIM-1. Sample collection and analysis as well as statistical evaluation of data have been conducted using well described methodologies. Multivariable regression models failed to identify significant associations of log-transformed glyphosate with any of the kidney injury biomarkers, controlling for covariates age, sex, and maternal education. The authors confirm detectability of glyphosate in children's urine at various ages and stages of life, there is no evidence in this study for renal injury in children exposed to low levels of glyphosate.

This publication is considered relevant for the risk assessment of glyphosate and reliable without restrictions because it complies with the quality criteria of a good monitoring study.

Title

公表文献調査報告書
グリホサート
別添資料 3
「区分 a」の文献に関する適合性及び信頼性判断理由

農作物及び畜産物への残留

(Summary of the literature data for Glyphosate: Appendix - Residues)

Date

2022-06-27

Author(s)

バイエルクロップサイエンス株式会社

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Short summary of relevant and reliable articles from category a) with / without restrictions)

Edition No.: M-812284-01-1

Author	El Agrebi Noemie Tosi Simone Wilmart Olivier Scippo Marie-Louise de Graaf Dirk C Saegerman Claude
Source	The Science of the total environment, (2020 Feb 20) Vol. 704, pp. 135312. Electronic Publication Date: 20 Nov 2019 Journal code: 0330500. E-ISSN: 1879-1026. L-ISSN: 0048-9697.
Title	Honeybee and consumer's exposure and risk characterisation to glyphosate-based herbicide (GBH) and its degradation product (AMPA): Residues in beebread, wax, and honey.
Publication Year	2019
Accession Number	2021844506 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

The article describes a survey of pesticide residues (glyphosate/AMPA) in various bee-related matrices (beebread, wax, honey) from Belgium. While the representativeness of the sampling procedures may be questioned and although the results of the analytical method validations are not provided in a high level of details, the results are considered reliable. A considerable number of samples of beebread/pollen (n = 82) and beeswax (n = 100) were analysed for parent glyphosate and its metabolite AMPA. However, according to the guideline SANTE/11956/2016 rev. 9 the intake of pollen and wax by consumers is negligible and, therefore, it is not a regulatory requirement to investigate the residue levels in these commodities. The publication also provides analytical results for 10 honey samples. Only one of these samples was found to contain residues of parent glyphosate above the LOQ of 0.010 mg/kg (at 0.011 mg/kg). None of the honey samples showed detectable residues of AMPA (i.e. these residues were < 0.001 mg/kg). Since according to SANTE/11956/2016 rev. 9 it is possible to derive MRLs in honey based on monitoring data, these results are deemed relevant.

The publication concludes that, based on the observed residue levels, the intake of pollen, beeswax and honey by consumers does not cause any health issue. While this conclusion is certainly correct some of the details of the risk assessment are questionable. For instance, the considered ADI of 0.3 mg/kg bw/day for parent glyphosate is obsolete (and was already obsolete at the time when the publication was issued). Furthermore, the long-term residue intakes were calculated based on maximum residue levels and high percentile consumption figures, which does not correspond to the standard approach.

The publication also includes extensive considerations on bee safety, which, however, are not relevant to this section of the dossier and, therefore, are not discussed here.

Edition No.: M-812257-01-1

Author	Thompson Thomas S; van den Heever Johan P; Limanowka Renata E
Source	Food additives & contaminants. Part A, Chemistry, analysis, control, exposure & risk assessment, (2019 Mar) Vol. 36, No. 3, pp. 434-446. Electronic Publication Date: 26 Feb 2019 Journal code: 101485040. E-ISSN: 1944-0057. L-ISSN: 1944-0057.
Title	Determination of glyphosate, AMPA, and glufosinate in honey by online solid-phase extraction-liquid chromatography-tandem mass spectrometry.
Publication Year	2019
Accession Number	2020876621 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

The article describes the development and validation of a method for the analysis of glyphosate, AMPA, and glufosinate in honey. Aqueous honey solutions were derivatised offline prior to direct analysis of the target analytes using online solid-phase extraction coupled to liquid chromatography-tandem mass spectrometry (LC-MS/MS). Method validation fulfil EU requirements. The method showed good performance for all analytes with a LOQ of 1 µg/kg for each analyte.

The method can be considered valid for monitoring purposes and has been applied for the analysis of two hundred randomly chosen honey samples from Canada. Virtually all the samples were found to contain measurable residues of glyphosate and/or AMPA, which is at least in part due to the extremely LOQ (1 µg/kg). The ratio between parent glyphosate and AMPA was very variable, which is also in contrast to the findings of the EU monitoring (where no measurable residues of AMPA were found) but may also be accounted for by the very low LOQ. In spite of the large number of samples analysed, none showed residues of parent glyphosate exceeding the current EU MRL of 0.05 mg/kg.

According to SANTE/11956/2016 rev. 9 it is possible to derive MRLs in honey based on monitoring data. As honey available to European consumers may originate from outside the EU, it is appropriate to consider honey residue data from outside the EU to derive the EU MRL. Therefore, the publication is considered relevant and reliable. It also includes a useful discussion of the residue levels of glyphosate in honey reported by other authors.

Edition No.: M-812258-01-1

Author	Chiesa Luca Maria; Nobile Maria; Panseri Sara; Arioli Francesco
Source	Food additives & contaminants. Part A, Chemistry, analysis, control, exposure & risk assessment, (2019 Apr) Vol. 36, No. 4, pp. 592-600. Electronic Publication Date: 14 Mar 2019 Journal code: 101485040. E-ISSN: 1944-0057. L-ISSN: 1944-0057.
Title	Detection of glyphosate and its metabolites in food of animal origin based on ion-chromatography-high resolution mass spectrometry (IC-HRMS).
Publication Year	2019
Accession Number	2020940032 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

The purpose of the publication is to describe and discuss the performance of a residue analytical method for glyphosate, AMPA and glufosinate in, food of animal origin. As such, the publication is not relevant to risk assessment. However, since it also reports residue levels for the investigated compounds in 10 honey samples and since according to SANTE/11956/2016 rev. 9 it is possible to derive EU MRLs in honey based on monitoring data, the publication may be considered relevant to risk assessment and MRL setting. Based on the provided validation results, the method is considered reliable. The LOQ (defined as the lowest fortification level yielding acceptable recoveries) was 0.010 mg/kg for both glyphosate and AMPA (although different values, presumably estimated from the signal to noise ratio, are stated in Table 2). None of the 10 analysed honey samples showed residues of glyphosate or AMPA above the LOQ. However, it is important to note that all the samples were from organic production and this may need to be taken into account in the evaluation.

Edition No.: M-813450-01-1

Author	Berg Carl J King H Peter Delenstarr Glenda Kumar Ritikaa Rubio Fernando; Glaze Tom
Source	PloS one, (2018) Vol. 13, No. 7, pp. e0198876. Electronic Publication Date: 11 Jul 2018 Journal code: 101285081. E-ISSN: 1932-6203. L-ISSN: 1932-6203. Report No.: PMC-PMC6040695.
Title	Glyphosate residue concentrations in honey attributed through geospatial analysis to proximity of large-scale agriculture and transfer off-site by bees.
Publication Year	2018
Accession Number	2020071133 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The publication provides residue levels for glyphosate in honey produced in Hawaii (majority of samples) but also Argentina, Brazil, Canada, Mexico, Uruguay and USA (mainland). It is considered relevant to the setting of a suitable MRL for glyphosate in honey since according to SANTE/11956/2016 rev. 9 it is possible to derive MRLs in honey based on monitoring data. As honey available to European consumers may originate from outside the EU, it is appropriate to consider honey residue data from outside the EU to derive the EU MRL.

The samples were analysed by means of an ELISA method which was validated indirectly by comparison with an LC-MS/MS method. A total of 14 honey samples were analysed with the two methods and the results were shown to be similar. The publication, however, does not provide validation data for the LC-MS/MS method (recovery rates from fortified samples).

The study showed a higher detection rate of glyphosate than in the EU-monitoring for 2016-2017. Besides the different origin of the samples, this may also be due to the use of different analytical methods with different LOQs. In line with the EU-monitoring the publication shows that glyphosate can occur in honey at levels > 0.05 mg/kg and that it is, therefore, appropriate to increase the existing EU-MRL. The highest measured residue level was 0.342 mg/kg, which is less than the maximum value found during the EU-monitoring for 2016-2017.

Edition No.: M-629607-01-1

Author	Karise Reet Raimets Risto; Williams Ingrid H; Mand Marika Bartkevics Vadims; Pugajeva Iveta Pihlik Priit; Viinalass Haldja Keres Indrek
Source	Chemosphere, (2017 Dec) Vol. 188, pp. 389-396. Electronic Publication Date: 4 Sep 2017 Journal code: 0320657. E-ISSN: 1879-1298. L-ISSN: 0045-6535.
Title	Are pesticide residues in honey related to oilseed rape treatments?.
Publication Year	2017
Accession Number	2018973890 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The publication is considered relevant to the setting of a suitable MRL for glyphosate in honey since according to SANTE/11956/2016 rev. 9 it is possible to derive MRLs in honey based on monitoring data. Although only limited information is given about the validation of the method for the determination of glyphosate residues, the analytical results are most likely reliable. The residue levels found for glyphosate are consistent with the EU-monitoring data published by EFSA for 2016-2017 in that: 1. Most of the samples do not show quantifiable residues of glyphosate. 2. Some samples show residues > 0.05 mg/kg, which indicates that it is appropriate to increase the existing MRL. 3. The measured residue levels are far below the levels found in the tunnel residue study.

Edition No.: M-812215-01-1

Author	Rubio Fernando, Guo Emily and Kamp Lisa
Source	Journal of Environmental and Analytical Toxicology (2014) 5: 249.
Title	Survey of Glyphosate Residues in Honey, Corn and Soy Products
Publication Year	2015
Accession Number	N/A
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

The article describes a survey of glyphosate residues in honey (n = 69), pancake and corn syrup (n = 26), soy sauce (n = 28), soy milk (n = 11) and tofu (n = 20) purchased in USA, but originating from various countries around the globe. In the context of the dossier for the renewal of the EU approval of glyphosate and with regard to the supported representative uses, the residue data for pancake and corn syrup, soy sauce, soy milk and tofu are not considered relevant. However, the residue data for glyphosate in honey are potentially relevant since according to the guideline SANTE/11956/2016 rev. 9 it is possible to derive MRLs in honey based on monitoring data. Only few of the analysed honey samples originated from Europe but, as honey available to European consumers may originate from outside the EU, it is appropriate to consider honey residue data from outside the EU to derive the EU MRL.

The samples were analysed by means of an ELISA method which was validated by determining the recovery rates from fortified samples. The validation results are not provided in detail, but the average recoveries and relative standard deviations were satisfactory, although the validation was not conducted exactly in accordance with EU or OECD guidelines (i.e. with at least 5 replicates at the LOQ and 5 replicates at a higher level). The limit of quantification was estimated at 0.015 mg/kg. The specificity of the method was investigated by assessing the response of the ELISA test to a series of substances chemically related to glyphosate and it was shown that the response of these substances was at least 1000 times less than that of glyphosate. While this experiment allows to exclude some possible sources of false-positive results, it does not allow to completely rule out that other (not tested compounds) may yield false positive results. Despite these limitations, the obtained analytical results are considered fairly reliable.

59 % percent of the 69 honey samples contained glyphosate residues above the method LOQ (0.015 mg/kg) with a concentration range between 0.017 and 0.163 mg/kg and a mean of 0.064 mg/kg. While the individual results are not provided, it seems that about 31 % of the samples (22 from 69) showed residues of glyphosate above the EU MRL of 0.05 mg/kg. The samples originating from the EU all showed residues < 0.05 mg/kg. Overall, the findings reported in the publication are in line with the results of the EU-monitoring since the publication shows that glyphosate can occur in honey at levels > 0.05 mg/kg and that it is, therefore, appropriate to increase the existing EU-MRL. The highest measured residue level was 0.163 mg/kg, which is less than the maximum value found during the EU-monitoring for 2016-2017.

Edition No.: M-813215-01-1

Author	Shehata, Awad A. [Reprint Author]; Schroedl, Wieland; Sehledorn, Philipp; Krueger, Monika
Source	Journal of Poultry Science, (JUL 2014) Vol. 51, No. 3, pp. 333-337. ISSN: 1346-7395.
Title	Distribution of Glyphosate in Chicken Organs and its Reduction by Humic Acid Supplementation.
Publication Year	2014
Accession Number	2014:600955 BIOSIS
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The publication provides information about the levels of parent glyphosate residues in feed and tissues of broiler chicken (including edible tissues such as muscle and liver). This may allow to estimate residue transfer factors from poultry feed to poultry meat. Therefore, the publication is considered relevant. The authors further investigated the impact of a feed supplementation with humic acid on the transfer of glyphosate residues in poultry tissues. It was concluded that the supplementation with humic acid allows to significantly decrease the residues of glyphosate in poultry tissues (-63 % in muscle and -28 % in liver). Thus, the control group (which received feed without humic acid supplementation) represents a worst case in terms of residues and is more relevant from a regulatory perspective. The highest residues found in chicken muscle and liver were extremely low (ca. 0.005 mg/kg and 0.018 mg/kg, respectively). This is consistent with the results of the submitted poultry feeding studies (which were conducted at dose levels far above the dietary exposure of the broiler chickens in the publication). However, both the experimental procedures and the obtained results are not described with a sufficient level of accuracy and it is difficult to figure out exactly what was done and how the presented results were generated. The sample preparation procedure (with consecutive steps at 100°C and -80°C) is quite unusual and no method validation data are presented. Because of that, the publication is reliable with restrictions.

Edition No.: M-813112-01-1

Author	Shelver, Weilin L.; Lupton, Sara J.; Shappell, Nancy W.; Smith, David J.; Hakk, Heldur
Source	ACS Omega, (2018) Vol. 3, No. 8, pp. 8697-8708. CODEN: ACSODF. ISSN: 2470-1343.
Title	Distribution of Chemical Residues among Fat, Skim, Curd, Whey, and Protein Fractions in Fortified, Pasteurized Milk
Publication Year	2018
Accession Number	2018:403787 TOXCENTER
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

The purpose of the described work was to investigate the partitioning of 12 environmental chemicals of diverse polarities into various milk fractions. One of the tested chemicals was glyphosate. The experiments were conducted with radio-labelled test materials which were fortified to raw (unpasteurised, non-homogenised) cow milk (3 fortification levels were investigated for each compound). Thereafter, the milk was processed into skim milk, milk fat, curd, whey, whey retentate and whey permeate. A linear model predicting the distribution of chemicals between skim milk and milk fat based on their lipophilicity was established. The distribution between curd and whey was also correlated with lipophilicity. Phenolic compounds had less predictable distribution patterns based on their lipophilicities.

During processing of whole milk to skim milk and milk fat, glyphosate partitioned essentially to skim milk (> 99 %). Only about 1 % of the glyphosate fortified to whole milk was recovered in milk fat. Following curding of the skim milk, most glyphosate remained in the whey fraction (> 80 %). The associations of glyphosate with whey protein (calculated by subtracting the amount present in permeate from the amount present in retentate) was very low (< 5 %). As expected due to its hydrophilicity, glyphosate primarily distributes into aqueous products, such as skim milk and whey. The distribution pattern between the various milk fractions was similar for the various amounts of glyphosate fortified to whole milk (range of ca. 0.004 mg/L to 0.348 mg/L).

Although the distribution of residues between skim milk and milk fat is not a data requirement for hydrophilic compounds like glyphosate, this information is considered relevant to risk assessment. Overall, the publication is deemed reliable. Normally, the distribution of residues between skim milk and milk fat should be investigated with raw milk containing incurred residues (in the context of metabolism or feeding studies) and not by (artificially) fortifying raw milk. However, due to the very low transfer of glyphosate-derived residues in milk, the approach used in the publication seems to be the best option to determine the distribution of parent glyphosate residues between skim milk and milk fat.

Edition No.: M-812219-01-1

Author	Schnabel Karina; Schmitz Rolf; von Soosten Dirk; Frahm Jana; Kersten Susanne; Meyer Ulrich; Danicke Sven Schnabel Karina; Schmitz Rolf; Breves Gerhard Hackenberg Rudolf; Spitzke Madeleine
Source	Archives of animal nutrition, (2017 Dec) Vol. 71, No. 6, pp. 413-427. Journal code: 101222433. E-ISSN: 1477-2817. L-ISSN: 1477-2817.
Title	Effects of glyphosate residues and different concentrate feed proportions on performance, energy metabolism and health characteristics in lactating dairy cows.
Publication Year	2017
Accession Number	2019185076 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

About 30 cows (distributed in two subgroups) were fed with glyphosate-treated commodities for 17 weeks. During this period the exposure of these cows to parent glyphosate residues via feed was about 0.110-0.120 mg/kg bw/day (Figure 1). None of the analysed milk samples (presumably about 60 pooled samples from the two subgroups fed with glyphosate-treated commodities) showed residues of parent glyphosate or AMPA above the limit of quantification of 0.01 mg/kg. This is fully in line with the results of the GLP cow feeding studies submitted in the dossier, which also show that the transfer (if any) of glyphosate-derived residues in cow milk is extremely low. Although the residue analytical method and residue analyses are not reported with a high level of detail, the results are considered reliable since the general principle of the described analytical procedures is well known and the validity of the residue determination was obviously demonstrated by suitable fortification trials. The publication, therefore, is considered relevant and reliable.

However, the main objective of the publication was to investigate the impact of glyphosate residues in feed on health and performance of dairy cows. No significant effects were identified but this part of the publication is not considered relevant to the residue section.

Edition No.: M-812455-01-1

Author	von Soosten D; Meyer U; Huther L; Danicke S Lahrssen-Wiederholt M; Schafft H; Spolders M Breves G
Source	Journal of dairy science, (2016 Jul) Vol. 99, No. 7, pp. 5318-5324. Electronic Publication Date: 20 Apr 2016 Journal code: 2985126R. E-ISSN: 1525-3198. L-ISSN: 0022-0302.
Title	Excretion pathways and ruminal disappearance of glyphosate and its degradation product aminomethylphosphonic acid in dairy cows.
Publication Year	2016
Accession Number	2016928162 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

The publication describes a series of 6 experiments in which dairy cows (n = 4-6 per experiment) were fed with glyphosate-treated feed for 26 days and where the excretion of parent glyphosate and AMPA residues via feces, urine and milk was investigated during the last 5 days of the experiments (i.e. at a time when steady state can be assumed). The intake of parent glyphosate residues ranged between < 0.001 mg/kg bw/day (experiments 4, 5 and 6) and 0.011 mg/kg bw/day (experiment 1) while the intake of AMPA residues ranged between < 0.001 mg/kg bw/day (experiments 4, 5 and 6) and about 0.008 mg/kg bw/day (experiment 1). These intake levels are far below the dose levels investigated in the goat metabolism studies and cow feeding studies submitted in the dossier (since the applicable guidelines require that the dose levels be higher) but are likely to reflect “typical” intake levels of dietary cows. In the experiments it was found that 50-73 % of ingested glyphosate was excreted in feces and 4-8 % in urine. Similarly, 44-50 % of ingested AMPA was excreted in feces and 8-12 % in urine (these figures assume that no glyphosate is metabolised to AMPA in the cows). These results are consistent with the results of the submitted goat metabolism studies which show that 47-78 % of the administered radioactivity is excreted via feces and 4.7-23 % via urine. The residues of parent glyphosate and AMPA in milk were below the limit of quantification of 0.01 mg/kg, which is consistent with the results of the GLP cow feeding studies submitted in the dossier. Although the residue analytical method and residue analyses are not reported with a high level of detail, the results are considered reliable since the general principle of the described analytical procedures is well known and the validity of the residue determination was obviously demonstrated by suitable fortification trials. The publication, therefore, is considered relevant and reliable.

Edition No.: M-812300-01-1

Author	Panseri Sara; Nobile Maria; Arioli Francesco; Chiesa Luca Maria Biolatti Cristina Pavlovic Radmila
Source	Food chemistry, (2020 Jun 04) Vol. 330, pp. 127205. Electronic Publication Date: 4 Jun 2020 Journal code: 7702639. E-ISSN: 1873-7072. L-ISSN: 0308-8146.
Title	Occurrence of perchlorate, chlorate and polar herbicides in different baby food commodities.
Publication Year	2020
Accession Number	2022581995 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

The article describes a monitoring of residues of glyphosate and AMPA in 105 commercially available baby food samples. The article is well described, the samples were analysed using validated analytical methods and the methodology is considered as reliable. The publications shows clearly absence of residues of glyphosate and AMPA in all tested commercially available baby food. This finding indicates that infants and toddlers that are mainly fed with ready-to-eat baby food are not exposed to significant levels of glyphosate or AMPA residues. However the finding cannot be directly related to the supported representative uses of glyphosate for renewal.

Edition No.: M-812223-01-1

Author	Zoller Otmar; Rhyn Peter; Rupp Heinz; Zarn Jurg A; Geiser Christoph
Source	Food additives & contaminants. Part B, Surveillance, (2018 Jun) Vol. 11, No. 2, pp. 83-91. Electronic Publication Date: 23 Jan 2018 Journal code: 101317183. E-ISSN: 1939-3229. L-ISSN: 1939-3210.
Title	Glyphosate residues in Swiss market foods: monitoring and risk evaluation.
Publication Year	2018
Accession Number	2019357998 MEDLINE
Overall reliability assessment	Uncertain reliability

Assessment and conclusion

The article describes the results of monitoring analyses for residues of glyphosate and AMPA in food conducted by Swiss authorities between 2012 and 2017. A total of 243 samples of diverse food commodities were analysed for glyphosate and AMPA using an LC-MS/MS method that was developed specifically by the Swiss monitoring laboratory. According to the authors the method has a limit of quantification of 0.001 mg/kg for parent glyphosate and 0.0025 mg/kg for AMPA in solid matrices and 0.0005 mg/kg and 0.001 mg/kg, respectively, in liquid matrices (beer, fruit juice, wine). While it seems that these LOQs were established according to recognised procedures, details are missing and it is, therefore, difficult to evaluate the reliability of the provided analytical results. This would be especially important since the reported LOQs are far below the LOQs achieved by most of the other official monitoring laboratories.

As stated by the authors the publication is not intended to provide a representative picture of the residues of glyphosate and AMPA in food commodities placed on the market in Switzerland since the commodities showing high residues were over-represented. In spite of that, the samples relevant to the uses supported in the renewal dossier (e.g. fruits, vegetables, fruit juice, wine, food of animal origin) all showed residues of glyphosate and AMPA far below 0.05 mg/kg (LOQ of most enforcement method so far).

In total, 16 honey samples from Europe and the Americas were analysed. They showed residues of parent glyphosate between < 0.001 mg/kg and 0.0159 mg/kg while the residues of AMPA were always < 0.0025 mg/kg (details are provided as supplementary data). Since according to SANTE/11956/2016 rev. 9 it is possible to derive EU MRLs in honey based on monitoring data and since honey marketed in Switzerland is likely to be also marketed in the EU, these results are deemed relevant to the setting of an EU MRL for glyphosate in honey. The fact that all the samples showed residues of AMPA < 0.0025 mg/kg is in contrast to another publication in which the analyses were also conducted with a very sensitive analytical method and where the residues of AMPA were often found at levels comparable to or even greater than the levels of parent glyphosate residues.

Title

公表文献調査報告書
グリホサート
別添資料 3
「区分 a」の文献に関する適合性及び信頼性判断理由

環境動態
(Summary of the literature data for Glyphosate: Appendix – Environmental Fate)

Date

2022-06-27

Author(s)

バイエルクロップサイエンス株式会社

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Short summary of relevant and reliable articles from category a) with / without restrictions)
Edition No.: M-812271-01-1

Author	Sun Mingjing; Li Hui Jaisi Deb P
Source	Water research, (2019 Oct 15) Vol. 163, pp. 114840. Electronic Publication Date: 4 Jul 2019 Journal code: 0105072. E-ISSN: 1879-2448. L-ISSN: 0043-1354.
Title	Degradation of glyphosate and bioavailability of phosphorus derived from glyphosate in a soil-water system
Publication Year	2019
Accession Number	2021387043 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article deals with aerobic soil degradation with non-labelled and stable-labelled glyphosate. AMPA formation was confirmed to occur as metabolite. The article focuses mainly on the fate of the phosphorous moiety to investigate for potential transformation products of glyphosate origin.
In general, the methods and results are described, but there is a lack of details reported to allow for the evaluation of all potential deviations from OECD 307. For example, soil properties are not reported, exact soil water content during incubation is unclear, the size/mass of soil samples incubated is not clearly stated (1 g soil was used for extraction). Further, procedures of work-up including procedural recoveries for glyphosate and AMPA are presented in figures, but not in detail (tabulated values). DT50 values according to SFO were calculated for glyphosate and AMPA (based on max. concentration) but no details on quality of fits and statistics are provided. No new transformation products were reported.
The article is therefore considered as reliable with restrictions.

Edition No.: M-812161-01-1

Author	Tauchnitz Nadine Kurzius Florian Rupp Holger; Meissner Ralph Schmidt Gerd Hauser Barbara Schrodter Matthias
Source	Environmental pollution (Barking, Essex : 1987), (2020 Dec) Vol. 267, pp. 115186. Electronic Publication Date: 11 Jul 2020 Journal code: 8804476. E-ISSN: 1873-6424. L-ISSN: 0269-7491.
Title	Assessment of pesticide inputs into surface waters by agricultural and urban sources - A case study in the Querne/Weida catchment, central Germany.
Publication Year	2020
Accession Number	2022948363 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
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 CaCl2 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.

Edition No.: M-813306-01-1

Author	Zhelezova Alena Zhelezova Alena Cederlund Harald; Stenstrom John
Source	Water, air, and soil pollution, (2017) Vol. 228, No. 6, pp. 216. Electronic Publication Date: 25 May 2017 Journal code: 0312676. ISSN: 0049-6979. L-ISSN: 0049-6979. Report No.: PMC-PMC5443863.
Title	Effect of Biochar Amendment and Ageing on Adsorption and Degradation of Two Herbicides.
Publication Year	2017
Accession Number	2018671916 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes the adsorption and degradation behavior of two agrochemicals in two agricultural soils from Northern Europe following amendment of biochar.

The tests resulted in data on adsorption and degradation of glyphosate in the presence and absence of biochar amended to soil samples.

The tests designs are described and the adsorption parameters are sufficiently reported. For adsorption experiments, conduct according to OECD guideline 106 is claimed for. However, validity criteria in terms of OECD Guideline 106 and the EU Evaluators Checklist could not checked due to a lack of such detail in reporting.

For the evaluation of the degradation tests, no information was reported in the publication whether a specific guideline was followed including details in design, conduct and analysis. The results were kinetically evaluated against Single First Order kinetics only to partly result in poor fits. No detailed information on findings at the different time points is reported thus preventing kinetic re-evaluation based on the presented data.

The article is therefore classified as reliable with restrictions.

Edition No.: M-813239-01-1

Author	Cassigneul A Benoit P; Bergheaud V; Dumeny V; Etievant V Goubard Y Maylin A; Alletto L Justes E
Source	The Science of the total environment, (2016 Mar 01) Vol. 545-546, pp. 582-90. Electronic Publication Date: 4 Jan 2016 Journal code: 0330500. E-ISSN: 1879-1026. L-ISSN: 0048-9697.
Title	Fate of glyphosate and degradates in cover crop residues and underlying soil: A laboratory study.
Publication Year	2016
Accession Number	2016596753 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes investigations on the degradation in and of adsorption of Glyphosate to soil under the potential influence by cover crops. The article is well described and provides potential endpoints for degradation and sorption. However, the available information does not allow to check the validity against current guidelines, and not enough parameters are provided to evaluate the kinetic behavior.
The article is therefore classified as reliable with restrictions.

Edition No.: M-813225-01-1

Author	Norgaard, Trine; de Jonge, Lis W; Moldrup, Per; Olsen, Preben; Johnsen, Anders R
Source	Water, air, and soil pollution (2015), Volume 226, Number 8, 262 p. ISSN: 0049-6979 Published by: Springer International Publishing Source Note: 2015 Aug., v. 226, no. 8
Title	Can Simple Soil Parameters Explain Field-Scale Variations in Glyphosate-, Bromoxyniloctanoate-, Diflufenican-, and Bentazone Mineralization?
Publication Year	2015
Accession Number	2015:376040 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article deals with investigations on mineralization in aerobic soil under laboratory and field conditions. Amongst other active substances, laboratory tests were performed with glyphosate.

In parallel the leaching behavior was investigated under field conditions for the soils used in laboratory tests on mineralization.

The study did not follow guidelines in design and conduct. Moreover, the level of detail of provided data does not allow for a check of validity of the study against current guidelines.

Furthermore, nor data on glyphosate content per sampling point, neither half-lives were provided.

The article is therefore classified as reliable with restrictions.

Edition No.: M-812433-01-1

Author	Kanissery Ramdas G; Welsh Allana; Sims Gerald K
Source	Journal of environmental quality, (2015 Jan) Vol. 44, No. 1, pp. 137-44. Journal code: 0330666. ISSN: 0047-2425. L-ISSN: 0047-2425.
Title	Effect of soil aeration and phosphate addition on the microbial bioavailability of carbon-14-glyphosate.
Publication Year	2015
Accession Number	2015485405 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes the sorption and degradation behavior of glyphosate in three different US soils under consideration of aerobic and anaerobic conditions and the addition of phosphates. The sorption experiment is well described stating that USEPA guidelines was followed. However, design, conduct and results are missing details in reporting (ads/des results at each concentration not available numerically) to allow for a check of validity.

A degradation test was conducted – being non-standard compared to Guideline OECD 307 - in a microcosm while again lacking of details in description of results to allow for the calculation of degradation or dissipation rates according to current EU guidance.

The article is therefore classified as reliable with restrictions.

Edition No.: M-812434-01-1

Author	Rampoldi E Ariel; Hang Susana; Barriuso Enrique
Source	Journal of environmental quality, (2014 Mar) Vol. 43, No. 2, pp. 558-67. Journal code: 0330666. ISSN: 0047-2425. L-ISSN: 0047-2425.
Title	Carbon-14-glyphosate behavior in relationship to pedoclimatic conditions and crop sequence.
Publication Year	2014
Accession Number	2015485598 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article investigates ^{14}C-glyphosate adsorption–desorption and degradation under different scenarios in relationship to soil properties and soil use applications. Three Argentinian sites/soils with varied pedoclimatic conditions and two crop sequences were selected. Sorption parameters and degradation in terms of mineralization are reported. Essential details to assess the quality of data, for example, in terms of the EU Evaluators Checklist, are not available, described, and there are some deviations from current guidelines. In addition, the pedo-climatic conditions do not correspond to EU conditions.
The article is therefore classified as reliable with restrictions.

Edition No.: M-813208-01-1

Author	Al-Rajab, A. J.; Hakami, O. M.
Source	American Journal of Environmental Sciences (2014), Volume 10, Number 2, pp. 94-101, 30 refs. ISSN: 1553-345X DOI: 10.3844/ajessp.2014.94.101 Published by: Science Publications, New York URL (Availability): http://thescipub.com/abstract/10.3844/ajessp.2014
Title	Behavior of the non-selective herbicide glyphosate in agricultural soil.
Publication Year	2014
Accession Number	2014:198925 CABA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article investigates the degradation/dissipation and the potential for mobility of glyphosate and its metabolite AMPA in three French soils. The soil degradation tests perfomed with ^{14}C-labelled glyphosate cannot be assesses fully for their quality and deviations from current guideline due to a lack of detail in reporting. This includes, for example, that no detailed values per sampling interval are reported for all soils. The semi-field leaching experiments were small-scale soil columns consisting of 35-cm with undisturbed soil with low diameter. It is a common observation that this design can cause preferential flow as some artifact thus having potential to result in false-positive findings in percolates of such type of 'lysimeter'. Being indicative in the best case, the results cannot be compared to those of 'full lysimeter studies' that are typically run for more than a year under outdoor conditons.

The article is therefore classified as reliable with restrictions.

Edition No.: M-813709-01-1

Author	Nghia Nguyen Khoi; Doerfler, U.; Suhadolc, M.; Gerhard, W.; Munch, J. C.; Schroll, R. Editor(s): Bakar, B. H.; Kurniadie, D.; Tjitrosoedirdjo, S.
Source	The role of weed science in supporting food security by 2020. Proceedings of the 24th Asian-Pacific Weed Science Society Conference, Bandung, Indonesia, October 22-25, 2013 (2013), pp. 312-324, 33 refs. ISBN: 978-602-96519-2-8 Published by: Weed Science S
Title	Soil properties governing biodegradation of the herbicide glyphosate in agricultural soils.
Publication Year	2013
Accession Number	2015:86234 CABA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the dissipation of glyphosate in agricultural soils in Europe. While a lot of experimental details are reported, the data are insufficient for kinetic evaluation since tests were run for 32 days in maximum only and determination of mineralization only, i.e. no detailed analysis for active substance and metabolites.
The article is therefore classified as reliable with restrictions.

Edition No.: M-812439-01-1

Author	Bergstrom, Lars; Borjesson, Elisabet; Stenstrom, John
Source	Journal of environmental quality (2011), Volume 40, Number 1, pp. 98-108 ISSN: 1537-2537 Published by: American Society of Agronomy, Crop Science Society of America, Soil Science Society Source Note: 2011 Jan., v. 40, no. 1
Title	Laboratory and Lysimeter Studies of Glyphosate and Aminomethylphosphonic Acid in a Sand and a Clay Soil
Publication Year	2011
Accession Number	2015:219729 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article investigates the behaviour of glyphosate and AMPA under conditions of outdoor lysimeters including the determination of sorption parameters and degradation data for two Swedish soils. The invesigations were performed with non-labelled test substances for which further information such as purity was not reported. The use of non-labelled test material does not allow for determination of mass balances. No detailed tabulated results per sample point are provided.

Lysimeter experiment: Not all required information is reported to allow for a check of the overall quality of the study.

Degradation and sorption tests: The tests for glyphosate were claimed to follow OECD 106 guideline while being unclear for soil degradation. Due to a lack of detail in reporting, information is insufficient to check the quality of data. In addition and for example, the LOD of the analytical methods used seem inappropriate to fulfill the requirements for EU data generation methods.

The article is therefore classified as reliable with restrictions for the three experiments.

Edition No.: M-812352-01-1

Author	Ghafoor A Jarvis N J; Thierfelder T; Stenstrom J
Source	The Science of the total environment, (2011 Apr 15) Vol. 409, No. 10, pp. 1900-8. Electronic Publication Date: 24 Feb 2011 Journal code: 0330500. E-ISSN: 1879-1026. L-ISSN: 0048-9697.
Title	Measurements and modeling of pesticide persistence in soil at the catchment scale.
Publication Year	2011
Accession Number	2011268753 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article investigates data of degradation and sorption tests performed for glyphosate on several Swedish agricultural soils. The analytical methods are not provided in detail, thus not allowing to check whether analytical methods could fulfill the requiremnts as set out for EU data generating methods including the appropriateness of LOD or LOQ. For the sorption experiment, no results are provided. No mass balances and measurement per sample date are provided for both experiments.
The article is therefore classified as reliable with restrictions.

Edition No.: M-812169-01-1

Author	Alexa, Ersilia [Reprint Author]; Sumalan, Renata; Negrea, Monica; Bragea, Mihaela; Poiana, Mariana-Atena; Radulov, Isidora; Lazureanu, Aurel
Source	Journal of Food Agriculture & Environment, (JUL-OCT 2010) Vol. 8, No. 3-4, Part 2, pp. 1193-1198. ISSN: 1459-0255.
Title	Studies on the biodegradation capacity of C-14-labelled glyphosate in vine plantation soils.
Publication Year	2010
Accession Number	2011:162523 BIOSIS
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article investigates the degradation of glyphosate in a European agricultural soil originating from vine in the laboratory. Only data on mineralisation are reported. Further data like mass balances, residues in soil and a half–life are not reported. The validity of the study cannot be evaluated due to missing information. The article is therefore classified as reliable with restrictions.

Edition No.: M-813129-01-1

Author	Al-Rajab Abdul Jabbar Schiavon Michel
Source	Journal of environmental sciences (China), (2010) Vol. 22, No. 9, pp. 1374-80. Journal code: 100967627. ISSN: 1001-0742. L-ISSN: 1001-0742.
Title	Degradation of 14C-glyphosate and aminomethylphosphonic acid (AMPA) in three agricultural soils.
Publication Year	2010
Accession Number	2011060250 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article investigates the soil degradation of glyphosate in three agricultural soils from the EU. The test was performed with radio-labelled and non-radiolabelled test substance. For the part dealing with radiolabeled test substance, only mineralisation was followed after application to soil. Deviations in conduct were the use of air–tight test vessels not allowing for air exchange; no information whether the applied test solution was mixed with the soil; $^{14}CO_2$ was passively (and potentially not quantitatively) collected; soil moisture was rather high (80 % of soil retention capacity). For the tests with non-radiolabelld test substance the details do not allow to assess the quality of the analytical method as EU data generating method including no LoD/LoQ provided. Only few results are reported quantitatively, mainly graphical plots; calculation method of DT_{50} not reported.

The article is therefore classified as reliable with restrictions.

Edition No.: M-813176-01-1

Author	Passeport Elodie Richard Benjamin; Chaumont Cedric; Margoum Christelle; Liger Lucie; Gril Jean-Joel; Tournebize Julien
Source	Environmental science and pollution research international, (2014 Apr) Vol. 21, No. 7, pp. 4883-94. Electronic Publication Date: 27 Apr 2013 Journal code: 9441769. E-ISSN: 1614-7499. L-ISSN: 0944-1344.
Title	Dynamics and mitigation of six pesticides in a "Wet" forest buffer zone.
Publication Year	2013
Accession Number	2013589292 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the mitigation of glyphosate among other pesticides by a wet forest buffer zone in France. Not all required parameters are reported to check validity of the study (e.g. information on test substance, analytical method, characterization of soil).
The article is classified as reliable with restrictions.

Edition No.: M-813288-01-1

Author	Todorovic, Gorana Rampazzo; Alexander Eder; Axel Mentler; Nicola Rampazzo; Peter Strauss; Winfried E H Blum
Source	International agrophysics (2014), Volume 28, Number 1, pp. 93-100 Published by: De Gruyter Open Source Note: 2014 Feb. 13, v. 28, no. 1
Title	Influence of soil tillage and erosion on the dispersion of glyphosate and aminomethylphosphonic acid in agricultural soils
Publication Year	2014
Accession Number	2017:98953 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes the runoff behavior of glyphosate and AMPA in two field experiments in two different European agricultural soils with artificial rainfall. No details on the description of the analytical method and of statistical analysis are provided.

In addition, water samples from percolation water and from two run-off retention basins were analyzed for glyphosate and AMPA but no details on experimental design, sampling or analytical method are given.

The article is therefore classified as reliable with restrictions for the runoff experiment while the results for percolation water and the run-off retention basins are considered not reliable.

Edition No.: M-812251-01-1

Author	Albers Christian Nyrop; Ernstsen Vibeke; Johnsen Anders Risbjerg
Source	Journal of environmental quality, (20190100) Vol. 48, No. 1, pp. 147-155. Journal code: 0330666. ISSN: 0047-2425. L-ISSN: 0047-2425.
Title	Soil Domain and Liquid Manure Affect Pesticide Sorption in Macroporous Clay Till.
Publication Year	2018
Accession Number	2020711341 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes the sorption behaviour of glyphosate to different soil domains (top- and sub-soils) from two agricultural soils in Denmark. The set-up of the experiment was based on the OECD 106 guideline but with significant deviations: The study was conducted with 1 mM $CaCl_2$ solution (standard: 10 mM solution), at 10°C (standard: 20 – 25 °C); at 4 test concentrations (standard: 5), no validation of the analytical methods used, no concentrations in the solid phase were explicitly reported, i.e. no mass balances or parental mass balances were established.

The article is therefore classified as reliable with restrictions i.e. not used in risk assessment.

Edition No.: M-812484-01-1

Author	Dollinger, Jeanne; Dages, Cecile; Samouelian, Anatja; Coulouma, Guillaume; Lanoix, Marthe; Blanca, Yves; Voltz, Marc
Source	Geoderma, (2018) Vol. 309, pp. 50-59. CODEN: GEDMAB. ISSN: 0016-7061.
Title	Contrasting soil property patterns between ditch bed and neighbouring field profiles evidence the need of specific approaches when assessing water and pesticide fate in farmed landscapes
Publication Year	2018
Accession Number	2018:501986 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports the properties of a soil from a ditch in an agricultural area in the south of France. Mainly, the hydraulic parameters of the different soil layers of the ditch and the surrounding banks are considered and modelled and tracer experiments with bromide are presented.
Sorption experiments with glyphosate were conducted and Freundlich sorption coefficients for the different soil horizons including topsoil and subsoil are reported. However, there was no detailed reporting of data to assess the validity (i.e. mass balances, chemical properties of test substance, solvents used, information about analytical methods and their validation including, LOD, LOQ, temperature, test concentrations, demonstration of stability of the test item).
The article is therefore classified as reliable with restrictions and was not used in risk assessment.

Edition No.: M-813277-01-1

Author	Skeff, Wael [Reprint Author]; Recknagel, Constantin; Duewel, Yvonne; Schulz-Bull, Detlef E.
Source	Marine Chemistry, (JAN 20 2018) Vol. 198, pp. 1-9. http://www.journals.elsevier.com/marine-chemistry/#description. CODEN: MRCHBD. ISSN: 0304-4203. E-ISSN: 1872-7581.
Title	Adsorption behaviors of glyphosate, glufosinate, aminomethylphosphonic acid, and 2-aminoethylphosphonic acid on three typical Baltic Sea sediments.
Publication Year	2018
Accession Number	2018:389869 BIOSIS
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the sorption of glyphosate and AMPA to sediments of the Baltic Sea. Sediments are out of scope of EU data requirements for adsorption data. There was no detailed reporting of data to assess the validity (i.e. mass balances, test items not sufficiently described, information about LOD, LOQ).

The article is therefore classified as reliable with restrictions and was not used in risk assessment.

Edition No.: M-812207-01-1

Author	Gomez Ortiz Ana Maria; Okada Elena Okada Elena; Costa Jose Luis Bedmar Francisco
Source	Environmental toxicology and chemistry, (20171000) Vol. 36, No. 10, pp. 2587-2592. Electronic Publication Date: 13 Sep 2017 Journal code: 8308958. E-ISSN: 1552-8618. L-ISSN: 0730-7268.
Title	Sorption and desorption of glyphosate in Mollisols and Ultisols soils of Argentina.
Publication Year	2017
Accession Number	2018549637 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes an adsorption/desorption experiment with glyphosate on three different agricultural soils from Argentina which have not been tested for their applicability to EU conditions due to the supportive character of the overall information in the article (insufficient information to assess validity, i.e. no mass balance, previous exposure to other chemicals not documented).

The article is therefore classified as reliable with restrictions and was not used in risk assessment.

Edition No.: M-812217-01-1

Author	Munira Sirajum; Farenhorst Annemieke
Source	Journal of environmental science and health. Part. B, Pesticides, food contaminants, and agricultural wastes, (2017 Dec 02) Vol. 52, No. 12, pp. 887-895. Electronic Publication Date: 29 Sep 2017 Journal code: 7607167. E-ISSN: 1532-4109. L-ISSN: 0360-1234
Title	Sorption and desorption of glyphosate, MCPA and tetracycline and their mixtures in soil as influenced by phosphate.
Publication Year	2017
Accession Number	2019036131 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes an OECD 106 experiment with glyphosate on a Canadian soil considering the influence of phosphate additions. The article shows some deviations from the validity criteria for EU guidelines (temperature, usage of 0.01 M KCl instead of 0.01 M CaCl2, no mass balance and no demonstration of test item stability).
The article is therefore classified as reliable with restrictions and was not used in risk assessment.

Edition No.: M-812495-01-1

Author	Munira, Sirajum; Annemieke Farenhorst; Wole Akinremi
Source	Geoderma (2017) ISSN: 0016-7061 Published by: Elsevier B.V. Source Note: 2017,
Title	Phosphate and glyphosate sorption in soils following long-term phosphate applications
Publication Year	2017
Accession Number	2018:64231 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a sorption experiment with phosphate and glyphosate to Canadian agricultural soils. Some validation criteria of the underlying OECD 106 study protocol were not met, or insufficient information is reported (i.e. no material balance, stability of test item not demonstrated, no pre-equilibration of samples).

The article is therefore classified as reliable with restrictions and was not used in risk assessment.

Edition No.: M-812454-01-1

Author	Munira Sirajum Farenhorst Annemieke; Flaten Don Grant Cynthia
Source	Chemosphere, (2016 Jun) Vol. 153, pp. 471-7. Electronic Publication Date: 29 Mar 2016 Journal code: 0320657. E-ISSN: 1879-1298. L-ISSN: 0045-6535.
Title	Phosphate fertilizer impacts on glyphosate sorption by soil.
Publication Year	2016
Accession Number	2016856979 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes a sorption experiment with glyphosate on a Canadian agricultural soil considering different treatments with phosphate fertilizer. Some information on soil and study design are not reported (i.e. soil characteristics, mass balances, amount of soil, no information on chromatographic methods used, stability of test item not demonstrated), so no final validity check is possible.

The article is therefore classified as reliable with restrictions. Therefore, data were not used in risk assessment.

Edition No.: M-813236-01-1

Author	Sidoli Pauline; Baran Nicole Sidoli Pauline; Angulo-Jaramillo Rafael
Source	Environmental science and pollution research international, (2016 Mar) Vol. 23, No. 6, pp. 5733-42. Electronic Publication Date: 19 Nov 2015 Journal code: 9441769. E-ISSN: 1614-7499. L-ISSN: 0944-1344.
Title	Glyphosate and AMPA adsorption in soils: laboratory experiments and pedotransfer rules.
Publication Year	2016
Accession Number	2016428559 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes batch adsorption experiments with glyphosate and AMPA on 17 soils from France. The OECD 106 guideline was considered. However, not all parameters were reported to check the validity of the study (i.e. no material and mass balances established, stability of test item not reported, chromatographic method for analysis of glyphosate not reported).

The article is therefore classified as reliable with restrictions and was not used in risk assessment.

Edition No.: M-813256-01-1

Author	Dollinger, Jeanne; Dages, Cecile; Voltz, Marc
Source	Environmental chemistry letters (2015), Volume 13, Number 3, pp. 293-307 ISSN: 1610-3653 Published by: Springer International Publishing Source Note: 2015 Sept., v. 13, no. 3
Title	Glyphosate sorption to soils and sediments predicted by pedotransfer functions
Publication Year	2015
Accession Number	2016:8101 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article estimates pedotransfer functions for the adsorption of glyphosate to soil based on review of existing published data. However, no new experimental data is presented neither existing data is evaluated regarding their quality in conduct according to OECD 106 or the EU Evaluators Checklist.

The article is therefore classified as reliable with restrictions, i.e. not used in risk assessment.

Edition No.: M-808790-01-1

Author	Tevez, Hector R. dos Santos Afonso, Maria (Reprint)
Source	BOLETIN DE LA SOCIEDAD GEOLOGICA MEXICANA, (2015) Vol. 67, No. 3, pp. 509-516. ISSN: 1405-3322.
Title	pH dependence of Glyphosate adsorption on soil horizons
Publication Year	2015
Accession Number	2016:832021 SCISEARCH
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the adsorption of non-labelled glyphosate to topsoil and subsoil of an agricultural soil from Argentina. The pH-dependency was investigated in addition. However, there was no detailed reporting of data to assess the validity (i.e. mass balances, detailed chemical properties of test substance, solvents used, information about analytical methods and their validation including, LOD, LOQ, temperature, test concentrations).

The article is therefore classified as reliable with restrictions, i.e. no use of data in risk assessment.

Edition No.: M-813228-01-1

Author	Jodeh, S.; Attallah, M.; Haddad, M.; Hadda, T. B.; Salghi, R.; Jodeh, D.; Warad, I.
Source	Journal of Materials and Environmental Science, (2014) Vol. 5, No. 6, pp. 2008-2016, 9 pp.. CODEN: JMESCN. ISSN: 2028-2508.
Title	Fate and mobility of glyphosate leachate in palestinian soil using soil column
Publication Year	2014
Accession Number	2015:27294 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a column leaching and adsorption tests with non-labelled glyphosate with a Palestinian agricultural soil.
Due to analytical method insensitivity, the lowest rate examined in the column leaching experiment was 5 times the yearly application rate. In addition, some essential information necessary for assessment of validity of both experiments is not reported (i.e. mass balances, equilibration solution not specified).

The article is classified as not reliable for the column leaching experiment and as reliable with restrictions for the adsorption experiment, i.e. it was not used in risk assessment.

Edition No.: M-812422-01-1

Author	Gjettermann, B; Petersen, C T; Hansen, S; Koch, C Bender; Styczen, M
Source	Soil Science Society of America journal (2011), Volume 75, Number 2, pp. 434-443 ISSN: 1435-0661 Published by: Soil Science Society Source Note: 2011 Mar., v. 75, no. 2
Title	Kinetics of Glyphosate Desorption from Mobilized Soil Particles
Publication Year	2011
Accession Number	2014:222182 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a leaching experiment with glyphosate in soil columns. The desorption of glyphosate from soil particles and its effect on interpretation of leaching experiments was in the focus of the study and desorption kinetics of particle-bound glyphosate are postulated to influence glyphosate transport strongly. Not all necessary information was reported to check the validity of the results (no mass balances, study set-up not clearly described, insufficient information on soil properties and soil origin, test item not sufficiently described, temperature not provided, molecular identity of desorbed radioactivity not determined).
The article is therefore classified as reliable with restrictions.

Edition No.: M-812186-01-1

Author	Gjettermann, B; Styczen, M; Koch, C B; Hansen, S; Petersen, C T
Source	Soil & sediment contamination (2011), Volume 20, Number 5-8, pp. 986-994 ISSN: 1058-8337 Source Note: 2011 , v. 20, no. 5-8
Title	Evaluation of Sampling Strategies for Pesticides in a Macroporous Sandy Loam Soil
Publication Year	2011
Accession Number	2016:1635 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a leaching experiment on soil columns with a dye and glyphosate (as well as pendimethalin). Glyphosate was only transported within a fraction of the stained soil volume. Some important information about study conditions are missing: agricultural use of the soil, temperature, soil parameters, details on analytics and on substance identification, sample storage conditions before analysis. The article is therefore classified as reliable with restrictions.

Edition No.: M-813484-01-1

Author	Gros Peter; Leinweber Peter Meissner Ralph; Rupp Holger Wirth Marisa A; Kanwischer Marion; Schulz-Bull Detlef E
Source	Environmental monitoring and assessment, (2020 Jan 21) Vol. 192, No. 2, pp. 127. Electronic Publication Date: 21 Jan 2020 Journal code: 8508350. E-ISSN: 1573-2959. L-ISSN: 0167-6369. Report No.: PMC-PMC6970956.
Title	Leaching and degradation of (13)C2-(15)N-glyphosate in field lysimeters.
Publication Year	2020
Accession Number	2022023594 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article reports results of a lysimeter experiment with 13C2 5N glyphosate in Germany. Besides analysis of lysimeter leachate, also soil and plant (maize) samples were analyzed. Although, the methods and results are well described, no endpoint can be derived due to some deviations from the relevant guideline (OECD 22). For example, it is not clear whether an undisturbed soil monolith has been used, and the origin and storage of soil is not reported. Amounts of precipitation are not reported in sufficient detail (only for 2 months) and amounts of leachate are only given as overall sum and weekly averages. glyphosate, the sensitivity of the analytical method is not reported (AMPA was analyzed only qualitatively), and the stability of analytes in leachates and extracts during frozen storage was not shown. Results of leachate analysis were not reported in µg/L (only as δ13C and δ15N), and results of soil analysis were only given in % of initial concentration.

The article is therefore considered as reliable with restrictions.

Edition No.: M-812306-01-1

Author	Albers Christian Nyrop Jacobsen Ole Stig Bester Kai; Jacobsen Carsten Suhr; Carvalho Pedro N
Source	Environmental pollution (Barking, Essex : 1987), (2020 Nov) Vol. 266, No. Pt 3, pp. 115225. Electronic Publication Date: 16 Jul 2020 Journal code: 8804476. E-ISSN: 1873-6424. L-ISSN: 0269-7491.
Title	Leaching of herbicidal residues from gravel surfaces - A lysimeter-based study comparing gravels with agricultural topsoil.
Publication Year	2020
Accession Number	2022855261 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
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.

Edition No.: M-812446-01-1

Author	Napoli Marco; Cecchi Stefano; Zanchi Camillo A; Orlandini Simone
Source	Journal of environmental quality, (2015 Sep) Vol. 44, No. 5, pp. 1667-73. Journal code: 0330666. ISSN: 0047-2425. L-ISSN: 0047-2425.
Title	Leaching of Glyphosate and Aminomethylphosphonic Acid through Silty Clay Soil Columns under Outdoor Conditions.
Publication Year	2015
Accession Number	2016292134 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes a lysimeter study with glyphosate using three lysimeters from the Chianti region in Italy. The study is well described, however, there is some information missing to check the validity of the study against current guidelines. The use of clay soil (low- to non-permeable soil) is considered not appropriate for lysimeter experiments, and from the information given in the article it cannot be excluded that the leaching may have been caused by preferential flow rather than percolation through the soil column. Further, there is no information available whether, apart from application, lysimeters were handled according to normal agricultural practice. From the information reported it is not possible to calculate annual mean concentrations in leachate for glyphosate and AMPA which would however be required in view of risk assessment.

The article is therefore classified as reliable with restrictions.

Edition No.: M-812391-01-1

Author	Ulen Barbro M Larsbo Mats; Kreuger Jenny K; Svanback Annika
Source	Pest management science, (2014 Mar) Vol. 70, No. 3, pp. 405-14. Electronic Publication Date: 13 Jun 2013 Journal code: 100898744. E-ISSN: 1526-4998. L-ISSN: 1526-498X. Report No.: NLM-PMC4238832; PMC-PMC4238832.
Title	Spatial variation in herbicide leaching from a marine clay soil via subsurface drains.
Publication Year	2014
Accession Number	2013619599 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a leaching experiment from a tile-drained Swedish marine clay soil with agricultural land use. Glyphosate among other herbicides was considered in analysis. Preferential transport in macropores was the dominant process for all investigated substances at the test site. Glyphosate losses in total were up to 0.23 %. The study provides supportive information but not all parameters to derive endpoints are reported.
The article is therefore classified as reliable with restrictions.

Edition No.: M-812441-01-1

Author	Ulen, Barbro; Alex, Gunborg; Kreuger, Jenny; Svanbaeck, Annika; Etana, Ararso
Source	Acta agriculturae Scandinavica (2012), pp. 241-251 ISSN: 1651-1913 Published by: Taylor & Francis Group Source Note: 2012 Nov. 1, v. 62, no. sup2
Title	Particulate-facilitated leaching of glyphosate and phosphorus from a marine clay soil via tile drains
Publication Year	2012
Accession Number	2015:40960 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a field leaching experiment with glyphosate in Sweden on an agriculturally used soil. At this particular site with a clay soil, vertical transport of glyphosate through macropores (preferential flow) is the main transport process. The article provides no information to check the validity against current standards. The article is therefore classified as reliable with restrictions.

Edition No.: M-812421-01-1

Author	Aronsson, H; Stenberg, M; Ulen, B
Source	Soil use and management (2011), Volume 27, Number 1, pp. 54-68 ISSN: 0266-0032 Published by: Blackwell Publishing Ltd Source Note: 2011 Mar., v. 27, no. 1
Title	Leaching of N, P and glyphosate from two soils after herbicide treatment and incorporation of a ryegrass catch crop
Publication Year	2011
Accession Number	2014:18007 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a 2-years leaching experiment in Sweden on two agricultural soils (one soil and one sand) with glyphosate. The method is not sufficiently described to evaluate the validity of the results. The article is therefore classified as reliable with restrictions.

Edition No.: M-812168-01-1

Author	Kjaer Jeanne Ernsten Vibeke; Jacobsen Ole H; Hansen Nis; de Jonge Lis Wollesen; Olsen Preben
Source	Chemosphere, (2011 Jul) Vol. 84, No. 4, pp. 471-9. Electronic Publication Date: 9 Apr 2011 Journal code: 0320657. E-ISSN: 1879-1298. L-ISSN: 0045-6535.
Title	Transport modes and pathways of the strongly sorbing pesticides glyphosate and pendimethalin through structured drained soils.
Publication Year	2011
Accession Number	2011614789 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes a leaching experiment with glyphosate and pendimethalin in a Danish tile-drained agricultural soil over eight months. The substance properties are sufficiently reported. Pesticide leaching from the unsaturated soil zone may occur as particle-facilitated transport via drain-connected macropores as lateral flow with strongly bound pesticides. With regard to the data requirement, the study is too short for a comprehensive evaluation of the leaching behavior. In addition, no residues were determined in different soil layers after finalization of the study, and sample storage stability prior to analysis was not established. The article is therefore classified as reliable with restrictions.

Edition No.: M-812164-01-1

Author	Candela Lucila Caballero Juan; Ronen Daniel
Source	The Science of the total environment, (2010 May 15) Vol. 408, No. 12, pp. 2509-16. Electronic Publication Date: 27 Mar 2010 Journal code: 0330500. E-ISSN: 1879-1026. L-ISSN: 0048-9697.
Title	Glyphosate transport through weathered granite soils under irrigated and non-irrigated conditions--Barcelona, Spain.
Publication Year	2010
Accession Number	2010269447 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes a leaching experiment with glyphosate in an agricultural area in Spain. Leaching over a period of several months in spring and in autumn was observed under irrigated and un–irrigated conditions. Glyphosate and AMPA were found in deeper soil layers than expected from the calculations based on a tracer experiment. Two possible explanation given were colloid-facilitated transport of glyphosate adsorbed by Al, Fe, oxides, hydroxides, organic matter and humic acids on one hand and preferential flow pathways driven by rainfall events or water application dose on the other hand. Without direct comparison of the timing and magnitude of the tracer in the actual field experiment the relevance of both processes cannot be assessed. Duration of the study was not long enough to evaluate the leaching behavior for a long–time perspective. Details regarding field sampling and sample handling practices and analysis are not sufficient to classify the study as fully reliable.

The article is therefore classified as reliable with restrictions.

Edition No.: M-813244-01-1

Author	Wang Shizong Seiwert Bettina; Reemtsma Thorsten Kastner Matthias; Miltner Anja Schaffer Andreas Yang Qi Nowak Karolina M
Source	Water research, (20160801) Vol. 99, pp. 91-100. Electronic Publication Date: 19 Apr 2016 Journal code: 0105072. E-ISSN: 1879-2448. L-ISSN: 0043-1354.
Title	(Bio)degradation of glyphosate in water-sediment microcosms - A stable isotope co-labeling approach.
Publication Year	2016
Accession Number	2016956269 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article reports the results from a water-sediment dissipation experiment with ^{13}C-^{15}N-labelled-glyphosate, conducted according to OECD guideline 308. The methods and results are generally well described and conclusive. However, the water and associated sediment were taken from a German small water body located in agricultural lowlands with continuous crop rotation and pesticide application, which is considered a high risk area for exposure to pesticides. Thus, it cannot be excluded that the water/sediment system received inputs of glyphosate or AMPA within the previous 4 years, as is required in OECD 308 guideline.

In addition, the use of stable-isotope enriched glyphosate does not allow to differentiate between applied substance and existing background. This is also documented by the fact that no metabolites were detected other than AMPA which is known for its potential stability under such test conditions.

In the main experiment, the application rate was extremely high (50 mg/L, equivalent to an application rate of 150 kg/ha when assuming overspray of a 30 cm deep water body) while in OECD 308 guideline it is recommended that the test concentration should be close to application rate or environmental concentrations. Hence the exaggerated test concentration may affect the route and rate of degradation.

The article is seen as reliable with restrictions and therefore supportive information.

Edition No.: M-813508-01-1

Author	Holtomo, Olivier; Mbigah, Manain Derrick; Nsangou, Mama; Motapon, Ousmanou
Source	RSC Advances (2021), 11(27), 16404-16418 CODEN: RSCACL; ISSN: 2046-2069
Title	Insight of UV-vis spectra and atmospheric implication for the reaction of OH radical towards glyphosate herbicide and its hydrates
Publication Year	2021
Accession Number	2021:1020012 HCAPLUS
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The aim of the study was the estimation of the atmospheric half-life of glyphosate considering reactions with OH-radical or Cl-atoms. The calculations yielded an atmospheric lifetime of glyphosate of 2.34 hours. The EU agreed method to determine the half-life of an active substance is the Atkinson approach. The calculation in the publication cannot be considered a common method and the endpoint should not supersede the endpoint calculated using the Atkinson method.
The study is considered reliable with restrictions.

Edition No.: M-813272-01-1

Author	Bento Celia P M Goossens Dirk Rezaei Mahrooz Riksen Michel; Ritsema Coen J; Geissen Violette Mol Hans G J
Source	Environmental pollution (Barking, Essex : 1987), (2017 Jan) Vol. 220, No. Pt B, pp. 1079-1089. Electronic Publication Date: 18 Nov 2016 Journal code: 8804476. E-ISSN: 1873-6424. L-ISSN: 0269-7491.
Title	Glyphosate and AMPA distribution in wind-eroded sediment derived from loess soil.
Publication Year	2017
Accession Number	2017693144 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes the glyphosate and AMPA distribution in wind-eroded sediment derived from a laboratory wind tunnel experiment with loess soil. The distribution of the substances in different particle size fractions is evaluated. Correlations to different soil parameters are presented. Methods and results are sufficiently described.

The article was seen as reliable.

Edition No.: M-813380-01-1

Author	Papagiannaki, Dimitra; Medana, Claudio; Binetti, Rita; Calza, Paola; Roslev, Peter [Reprint Author]
Source	Scientific Reports, (NOV 20 2020) Vol. 10, No. 1, pp. Article No.: 20247. http://www.nature.com/srep. ISSN: 2045-2322. E-ISSN: 2045-2322.
Title	Effect of UV-A, UV-B and UV-C irradiation of glyphosate on photolysis and mitigation of aquatic toxicity.
Publication Year	2020
Accession Number	2021:95722 BIOSIS
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
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.

Edition No.: M-813507-01-1

Author	Geissen Violette; Oostindie Klaas; Bin Zhaoqi; Pyne Erin; Busink Sjors; Ritsema Coen J Silva Vera Lwanga Esperanza Huerta Beriot Nicolas Zomer Paul; Mol Hans
Source	Environmental pollution (Barking, Essex : 1987), (2021 Jun 01) Vol. 278, pp. 116827. Electronic Publication Date: 8 Mar 2021 Journal code: 8804476. E-ISSN: 1873-6424. L-ISSN: 0269-7491.
Title	Cocktails of pesticide residues in conventional and organic farming systems in Europe - Legacy of the past and turning point for the future.
Publication Year	2021
Accession Number	2023800535 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
In this study several compounds, including glyphosate and AMPA, were analysed in 340 agricultural topsoil samples from 4 representative EU study sites in Spain, Portugal and the Netherlands. Soil samples were collected between 2015 and 2018 after harvest or before the start of the growing season.

No information on the sampling procedure and storage time of the topsoil samples is provided. This does not allow to assess the representativeness of the soil samples. Furthermore, only maximum and median values are reported and the results cannot be assigned to a respective sampling period.
Therefore, the article is considered reliable with restrictions.

Edition No.: M-813561-01-1

Author	Piel Stephanie; Grandcoin Alexis; Baures Estelle
Source	Journal of environmental science and health. Part. B, Pesticides, food contaminants, and agricultural wastes, (2021 Feb 09) pp. 1-17. Electronic Publication Date: 9 Feb 2021 Journal code: 7607167. E-ISSN: 1532-4109. L-ISSN: 0360-1234.
Title	Understanding the origins of herbicides metabolites in an agricultural watershed through their spatial and seasonal variations.
Publication Year	2021
Accession Number	2023617131 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article reports concentrations of glyphosate and AMPA found in 12 wells used for drinking water consumption in Northern Italy, situated within a wine growing area. Traces of glyphosate (maximum reached 0.08 µg/L) and AMPA (maximum reached 0.25 µg/L) were detected in 2 wells supplying an urban area. The article is therefore considered as reliable with restrictions. Sampling and analytical methods are not described. Nature of groundwater wells not described, point sources could be possible. No information on precipitation is reported. No description of monitoring sites other than very rough map of area and aqueduct names.

Edition No.: M-813315-01-1

Author	Karanasios, Evangelos; Karasali, Helen; Marousopoulou, Anna; Akrivou, Antigoni; Markellou, Emilia
Source	Environmental Monitoring and Assessment, (2018) Vol. 190, No. 6, pp. 1-15. CODEN: EMASDH. ISSN: 0167-6369.
Title	Monitoring of glyphosate and AMPA in soil samples from two olive cultivation areas in Greece: aspects related to spray operators activities
Publication Year	2018
Accession Number	2018:291220 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports monitoring data for glyphosate and AMPA in Greek agricultural soils associated with olive production. Glyphosate and AMPA were present at maximum concentrations of 350 and 650 µg/kg, respectively.
The article is therefore considered reliable.

Edition No.: M-812489-01-1

Author	Silva, Vera; Arwyn Jones; Coen J Ritsema; Hans G J Mol; Luca Montanarella; Oihane FernAXA1ndez-Ugalde; Violette Geissen
Source	Science of the total environment (2017) ISSN: 0048-9697 Published by: Elsevier B.V. Source Note: 2017,
Title	Distribution of glyphosate and aminomethylphosphonic acid (AMPA) in agricultural topsoils of the European Union
Publication Year	2018
Accession Number	2018:5053 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the result from a field study to measure the distribution of glyphosate and AMPA in European topsoils. The study should give a basis for the understanding of glyphosate loss from soils via wind and water erosion, i.e. experimental information from the sample sites were extrapolated to the EU area. A detailed and tabulated overview on the results is given in the supporting information. The maximum measured concentrations of 2.05 mg/kg for glyphosate and 1.92 mg/kg for AMPA were from vineyards in central Portugal.
The article is therefore considered reliable with restrictions.

Edition No.: M-812189-01-1

Author	Napoli Marco; Marta Anna Dalla; Zanchi Camillo A; Orlandini Simone
Source	Journal of environmental quality, (2016 Sep) Vol. 45, No. 5, pp. 1713-1721. Journal code: 0330666. ISSN: 0047-2425. L-ISSN: 0047-2425.
Title	Transport of Glyphosate and Aminomethylphosphonic Acid under Two Soil Management Practices in an Italian Vineyard.
Publication Year	2016
Accession Number	2017455832 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a runoff experiment with glyphosate in a vineyard in Italy. The runoff was measured for glyphosate and AMPA residues. Maximum concentrations of glyphosate and AMPA dissolved in runoff were 128.9 µg/L and 151.9 µg/L, respectively. Maximum concentrations of glyphosate and AMPA associated with runoff sediment were 680 µg/kg and 710 µg/kg respectively.

Soil residues after 12 months were also assessed. No extractable glyphosate was detected in the soil profiles. The maximum AMPA concentration was 65.5 ± 6 µg/kg measured in the top 5 cm of a permanently grassed vineyard soil 0 m from the row.

The article is therefore considered reliable.

Edition No.: M-813231-01-1

Author	Szekacs, Andras (Reprint) Szekacs, Andras (Reprint); Moertl, Maria; Fekete, Gabor; Fejes, Agnes; Darvas, Bela Dombos, Miklos; Szecsy, Orsolya; Anton, Attila
Source	CARPATHIAN JOURNAL OF EARTH AND ENVIRONMENTAL SCIENCES, (AUG 2014) Vol. 9, No. 3, pp. 47-60. ISSN: 1842-4090.
Title	MONITORING AND BIOLOGICAL EVALUATION OF SURFACE WATER AND SOIL MICROPOLLUTANTS IN HUNGARY
Publication Year	2014
Accession Number	2015:65154 SCISEARCH
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports measurements of glyphosate among other pesticides, organic pollutants, heavy metals and other microelements in soils, surface waters and groundwater bodies in Hungary from agricultural and industrial settings. The effect of the found concentrations of the different substance on *D. magna* was investigated. The reported glyphosate findings cannot be assigned to the respective sampling site. Furthermore, no comprehensive list of glyphosate findings is presented. A maximum concentration of glyphosate at 0.98 µg/L was reported as an unspecified (SW/GW) water contaminant. The maximum glyphosate soil concentration reported was 0.56 ± 0.26 mg/kg.
The article is therefore considered reliable with restrictions.

Edition No.: M-812392-01-1

Author	Daouk Silwan De Alencastro Luiz F; Pfeifer Hans-Rudolf
Source	Journal of environmental science and health. Part. B, Pesticides, food contaminants, and agricultural wastes, (2013) Vol. 48, No. 9, pp. 725-36. Journal code: 7607167. E-ISSN: 1532-4109. L-ISSN: 0360-1234.
Title	The herbicide glyphosate and its metabolite AMPA in the Lavaux vineyard area, western Switzerland: proof of widespread export to surface waters. Part II: the role of infiltration and surface runoff.
Publication Year	2013
Accession Number	2013653314 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports the mobility of glyphosate and AMPA in soil after application of the parent to a vineyard soil in Switzerland. The maximum reported soil pore water concentrations were <14 µg/L and <8 µg/L (inferred from figure) for glyphosate and AMPA, respectively. The loss to surface waters via surface runoff and throughflows in soils with subsequent exfiltration to surface waters was considered. The reported parameters are insufficient to allow a complete assessment of the validity of the study.
The article is therefore considered reliable with restrictions.

Edition No.: M-813517-01-1

Author	Rosenbom, Annette E.; Olsen, Preben; Plauborg, Finn; Grant, Ruth; Juhler, Rene K.; Brusch, Walter; Kjaer, Jeanne
Source	Environmental Pollution (Oxford, United Kingdom), (2015) Vol. 201, pp. 75-90. CODEN: ENPOEK. ISSN: 0269-7491.
Title	Pesticide leaching through sandy and loamy fields - Long-term lessons learnt from the Danish Pesticide Leaching Assessment Programme
Publication Year	2015
Accession Number	2015:389402 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article is issued by the Danish Ministry of Energy, Utilities and Climate. The research program PLAP has high quality assurance measures.
The article is considered reliable.

Edition No.: M-813286-01-1

Author	Poiger Thomas; Buerge Ignaz J; Bachli Astrid; Muller Markus D; Balmer Marianne E
Source	Environmental science and pollution research international, (2017 Jan) Vol. 24, No. 2, pp. 1588-1596. Electronic Publication Date: 27 Oct 2016 Journal code: 9441769. E-ISSN: 1614-7499. L-ISSN: 0944-1344.
Title	Occurrence of the herbicide glyphosate and its metabolite AMPA in surface waters in Switzerland determined with on-line solid phase extraction LC-MS/MS.
Publication Year	2017
Accession Number	2017603245 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the derivation of a simplified procedure for the determination of glyphosate and AMPA in water samples. More than 1000 samples from ground and surface waters, and from treated wastewaters in Switzerland were tested with this method and the results are reported.
The article is considered reliable.

Edition No.: M-812456-01-1

Author	Di Guardo, Andrea; Finizio, Antonio
Source	Science of the Total Environment, (2016) Vol. 545-546, pp. 200-209. CODEN: STENDL. ISSN: 0048-9697.
Title	A moni-modeling approach to manage groundwater risk to pesticide leaching at regional scale
Publication Year	2016
Accession Number	2016:15115 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article presents an approach for combining long-term groundwater monitoring data from the Lombardy Region, Northern Italy with regional scale vulnerability modelling. No experimental or monitoring data were generated.

The 95th percentile monitoring values indicate that the groundwater concentrations of glyphosate ranged between 0.04 – 0.06 µg/L in 280 wells (98 %) and greater than the parametric drinking water limit of 0.1 µg/L in 5 wells (2 %).

The article is considered reliable with restrictions.

Edition No.: M-813213-01-1

Author	McManus, Sarah-Louise; Richards, Karl G.; Grant, Jim; Mannix, Anthony; Coxon, Catherine E.
Source	Environmental Monitoring and Assessment, (2014) Vol. 186, No. 11, pp. 7819-7836. CODEN: EMASDH. ISSN: 0167-6369.
Title	Pesticide occurrence in groundwater and the physical characteristics in association with these detections in Ireland
Publication Year	2014
Accession Number	2014:343552 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports the evaluation of a two-years national groundwater monitoring campaign in Ireland. Methods and results are sufficiently described.
The article is considered reliable.

Edition No.: M-813196-01-1

Author	Norgaard, Trine; Olsen, Preben; de Jonge, Lis W.; Moldrup, Per; Ferre, Ty P. A.; Rosenbom, Annette E.
Source	Vadose Zone Journal; Vadose Zone Journal (1 Oct 2014) Volume 13, Number 10, 18 p., 48 refs. DOI: 10.2136/vzj2014.05.0054 Published by: Soil Science Society of America,
Title	Leaching of Glyphosate and Aminomethylphosphonic Acid from an Agricultural Field over a Twelve-Year Period
Publication Year	2014
Accession Number	2014520701 ESBIOBASE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article reports the results of a 12-year field-scale monitoring program on the leaching of glyphosate and AMPA in Denmark. The analytical method 8270 applied between 2007 and 2010 showed insufficient recovery. The correction procedure by a constant factor of 2 is considered not appropriate in the context of the active substance approval under Regulation (EC) No 1107/2009. Further, it is discussed that measurements in the drainflow may origin from drainage of surface water as well as from groundwater, i.e. a clear conclusion about drained substance amounts cannot be drawn. As the overall results of the article may add valuable supplementary information to the data set.
The article is considered reliable with restrictions.

Edition No.: M-467952-01-1

Author	Moertl, Maria; Nemeth, Gyoengyi; Juracsek, Judit; Darvas, Bela; Kamp, Lisa; Rubio, Fernando; Szekacs, Andras
Source	Microchemical Journal (2013), Volume 107, pp. 143-151 ISSN: 0026-265X Published by: Elsevier B.V. Source Note: 2013 Mar., v. 107
Title	Determination of glyphosate residues in Hungarian water samples by immunoassay
Publication Year	2013
Accession Number	2015:358224 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a monitoring study where immunoassay analytical method was used. Several findings in different compartments (surface waters, ground water) were reported. Methods and results are sufficiently described.
The article is considered reliable.

Edition No.: M-468019-01-1

Author	Sanchis Josep Kantiani Lina; Llorca Marta; Rubio Fernando; Ginebreda Antoni; Fraile Josep; Garrido Teresa; Farre Marinella
Source	Analytical and bioanalytical chemistry, (2012 Mar) Vol. 402, No. 7, pp. 2335-45. Electronic Publication Date: 20 Nov 2011 Journal code: 101134327. E-ISSN: 1618-2650. L-ISSN: 1618-2642.
Title	Determination of glyphosate in groundwater samples using an ultrasensitive immunoassay and confirmation by on-line solid-phase extraction followed by liquid chromatography coupled to tandem mass spectrometry.
Publication Year	2012
Accession Number	2012245114 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article presents an analytical method to determine glyphosate in groundwater samples from Catalonia / Spain. Glyphosate findings in the respective groundwater samples are presented. Methods and results are well described. Maximum concentration of glyphosate measured at 2560 ng/L in 2010.
The article is considered reliable.

Edition No.: M-813164-01-1

Author	Bruchet, Auguste; Robert, Samuel; Esperanza, Mar; Janex-Habibi, Marie-Laure; Miege, Cecile; Coquery, Marina; Budzinski, Helene; Lemenach, Karine
Source	European Journal of Water Quality, (2011) Vol. 42, No. 2, pp. 123-133. CODEN: EJWQAT. ISSN: 1818-8710.
Title	Natural attenuation of priority and emerging contaminants during river bank filtration and artificial recharge
Publication Year	2011
Accession Number	2012:565280 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a monitoring experiment with glyphosate and AMPA among different other substances from Seine river and a drinking water production area downstream of the Paris urban area. The study is well described, the analytical methods used are sufficient.

With respect to glyphosate and AMPA, the study sheds light on the effectiveness of the water treatment train employed for a major surface water to drinking water plant, where the primary treatment process is bank filtration. In this case, it is clear that bank filtration has been shown to be an effective process to remove glyphosate and AMPA to <0.1 µg/L from water destined to be drinking water.

The article is considered reliable.

Edition No.: M-812471-01-1

Author	Di Guardo, Andrea; Antonio Finizio
Source	Science of the total environment (2017) ISSN: 0048-9697 Published by: Elsevier B.V. Source Note: 2017,
Title	A new methodology to identify surface water bodies at risk by using pesticide monitoring data: The glyphosate case study in Lombardy Region (Italy)
Publication Year	2018
Accession Number	2017:438027 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article presents an approach for combining long-term surface water monitoring data from the Lombardy Region of Northern Italy with GIS analysis to identify contamination levels and implement pesticide risk mitigation measures for surface water bodies No experimental or monitoring data were generated. The measured maximum concentration of glyphosate was 108 µg/L in 2013.
The article is considered reliable with restrictions.

Edition No.: M-812226-01-1

Author	Huntscha Sebastian; Buhlmann Andreas; Ahrens Christian H; Frey Jurg E; Buerge Ignaz J; Balmer Marianne E; Poiger Thomas Stravs Michael A; Pomati Francesco; Hollender Juliane Stravs Michael A; Hollender Juliane Ahrens Christian H Pomati Francesco
Source	Environmental science & technology, (2018 Apr 17) Vol. 52, No. 8, pp. 4641-4649. Electronic Publication Date: 27 Mar 2018 Journal code: 0213155. E-ISSN: 1520-5851. L-ISSN: 0013-936X.
Title	Seasonal Dynamics of Glyphosate and AMPA in Lake Greifensee: Rapid Microbial Degradation in the Epilimnion During Summer.
Publication Year	2018
Accession Number	2019656284 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the concentrations of glyphosate and AMPA in lake Greifensee in Switzerland representing a catchment with high portion of agricultural land use. The maximum concentration of glyphosate in samples from the two main tributaries of the lake was 1430 ng/L. Maximum glyphosate concentration in treated wastewater discharging into the lake was 350 ng/L. The maximum AMPA concentration in the two main tributaries was 415 ng/L. Concentrations in treated wastewater reached up to 1680 ng/L. For lake Greifensee, concentration of glyphosate reached a maximum of 145 ng/L in the epilimnion, and concentration of AMPA reached a maximum of 130 ng/L in the hypolimnion.

The article is considered reliable.

Edition No.: M-813445-01-1

Author	Masiol Mauro Gianni Biagio; Prete Marco
Source	Environmental science and pollution research international, (2018 Aug) Vol. 25, No. 24, pp. 24368-24378. Electronic Publication Date: 15 Jun 2018 Journal code: 9441769. E-ISSN: 1614-7499. L-ISSN: 0944-1344.
Title	Herbicides in river water across the northeastern Italy: occurrence and spatial patterns of glyphosate, aminomethylphosphonic acid, and glufosinate ammonium.
Publication Year	2018
Accession Number	2020024118 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports measurements of glyphosate and AMPA in surface waters in Northern Italy. Maximum surface water glyphosate concentration measured at 0.72 µg/L, and maximum AMPA concentration at 0.77 µg/L.
The article is considered reliable.

Edition No.: M-813111-01-1

Author	Dairon, R.; Dutertre, A.; Tournebize, J.; Marks-Perreau, J.; Carluer, N.
Source	Environmental Science and Pollution Research (2017), 24(8), 6866-6877 CODEN: ESPLEC; ISSN: 0944-1344
Title	Long-term impact of reduced tillage on water and pesticide flow in a drained context
Publication Year	2017
Accession Number	2017:126944 HCAPLUS
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes the different long-term drainage behavior of glyphosate among other pesticides under reduced tillage and conventional tillage at the experimental station of La Jaillière located in western France. Influence of more than 20 years (1988‑2010) of reduced tillage practices on water and pesticide balances and dynamics is analyzed and compared to results from a conventional tillage plot. The maximum glyphosate concentration in drainflow was observed on the conventional tillage plot 2 days after winter application with a value of 12 µg/L.

The article is considered reliable with restrictions.

Edition No.: M-589692-01-1

Author	Lefrancq Marie Jadas-Hecart Alain; Landry David La Jeunesse Isabelle Payraudeau Sylvain
Source	The Science of the total environment, (2017 Jun 01) Vol. 587-588, pp. 75-86. Electronic Publication Date: 24 Feb 2017 Journal code: 0330500. E-ISSN: 1879-1026. L-ISSN: 0048-9697.
Title	High frequency monitoring of pesticides in runoff water to improve understanding of their transport and environmental impacts.
Publication Year	2017
Accession Number	2018310817 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports the results from a runoff experiment in a French vineyard with different pesticides with a high-frequency setup. Data on glyphosate and AMPA were measured and reported.
The article is considered reliable.

Edition No.: M-813281-01-1

Author	Lerch, R. N.; Lin, C. H.; Goyne, K. W.; Kremer, R. J.; Anderson, S. H.
Source	Journal of the American Water Resources Association (2017), Volume 53, Number 3, pp. 667-683 ISSN: 1093-474X DOI: 10.1111/1752-1688.12526 Published by: American Water Resources Association (AWRA), Middleburg URL (Availability): http://onlinelibrary.wiley.
Title	Vegetative buffer strips for reducing herbicide transport in runoff: effects of buffer width, vegetation, and season.
Publication Year	2017
Accession Number	2017:274247 CABA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a runoff experiment to evaluate the effectiveness of vegetative buffer strips in USA. The article is considered reliable with restrictions.

Edition No.: M-642990-01-1

Author	Mottes Charles Lesueur Jannoyer Magalie Le Bail Marianne Guene Mathilde; Carles Celine Malezieux Eric
Source	Chemosphere, (2017 Oct) Vol. 184, pp. 762-773. Electronic Publication Date: 16 Jun 2017 Journal code: 0320657. E-ISSN: 1879-1298. L-ISSN: 0045-6535.
Title	Relationships between past and present pesticide applications and pollution at a watershed outlet: The case of a horticultural catchment in Martinique, French West Indies.
Publication Year	2017
Accession Number	2018709357 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the monitoring of glyphosate among several pesticides in a horticultural catchment in Martinique, French West India (part of the EU). Methods and results are well described.
The article is considered reliable.

Edition No.: M-812460-01-1

Author	Reoyo-Prats, Brice; Aubert, Dominique; Menniti, Christophe; Ludwig, Wolfgang; Sola, Jennifer; Pujo-Pay, Mireille; Conan, Pascal; Verneau, Olivier; Palacios, Carmen
Source	Science of the Total Environment, (2017) Vol. 579, pp. 10-21. CODEN: STENDL. ISSN: 0048-9697.
Title	Multicontamination phenomena occur more often than expected in Mediterranean coastal watercourses: Study case of the Tet River (France)
Publication Year	2017
Accession Number	2016:533256 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports the contamination scheme of a Mediterranean river with different pollutant, among others glyphosate and AMPA. The considered approach identified that high concentrations peaks are caused by specific weather conditions, e.g. heavy rainfall after a dry period with consecutive overflow of WWTP, and other sources. The experiment does not focus explicitly on agricultural conditions. Maximum glyphosate and AMPA concentrations measured at 1.500 µg/L and 1.702 µg/L, respectively.
The article is considered reliable with restrictions.

Edition No.: M-813268-01-1

Author	Desmet N Touchant K; Bronders J Seuntjens P Tang T
Source	The Science of the total environment, (2016 Dec 15) Vol. 573, pp. 1580-1588. Electronic Publication Date: 4 Oct 2016 Journal code: 0330500. E-ISSN: 1879-1026. L-ISSN: 0048-9697.
Title	A hybrid monitoring and modelling approach to assess the contribution of sources of glyphosate and AMPA in large river catchments.
Publication Year	2016
Accession Number	2017473876 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports a hybrid monitoring and modelling approach to evaluate different sources of glyphosate and AMPA in the Meuse River in the Netherlands and their decay in the waterbody. Waste-water treatment plants and tributaries were considered as entry routes of the substances. The experiment does not consider or model explicitly the contribution of agricultural application of the substances. The measured maximum concentrations of glyphosate in the river Meuse was 0.7 µg/L and in its tributaries was 12 µg/L. Also, the measured maximum concentrations of AMPA in the river Meuse was 3 µg/L and in its tributaries was 130 µg/L.
The article is considered reliable with restrictions.

Edition No.: M-629588-01-1

Author	Larsbo Mats; Sandin Maria; Jarvis Nick; Etana Ararso; Kreuger Jenny
Source	Journal of environmental quality, (2016 Jul) Vol. 45, No. 4, pp. 1367-74. Journal code: 0330666. ISSN: 0047-2425. L-ISSN: 0047-2425.
Title	Surface Runoff of Pesticides from a Clay Loam Field in Sweden.
Publication Year	2016
Accession Number	2017186813 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a runoff experiment on a field site in Sweden with realistic cultivation conditions. The runoff of glyphosate and AMPA was measured over a period of 3 years.
The article is considered reliable.

Edition No.: M-622676-01-1

Author	Schreiner, Verena C.; Szoecs, Eduard; Bhowmik, Avit Kumar; Vijver, Martina G.; Schaefer, Ralf B.
Source	Science of the Total Environment, (2016) Vol. 573, pp. 680-689. CODEN: STENDL. ISSN: 0048-9697.
Title	Pesticide mixtures in streams of several European countries and the USA
Publication Year	2016
Accession Number	2016:416914 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article summarizes monitoring results of pesticides in some EU Member States and the USA. Glyphosate measurements were derived from databases of national or regional government agencies in Germany, France, the Netherlands and the USA and were reported and evaluated.
The article is considered reliable.

Edition No.: M-530452-01-1

Author	Stenrod, Marianne (Reprint)
Source	ACTA AGRICULTURAE SCANDINAVICA SECTION B-SOIL AND PLANT SCIENCE, (30 APR 2015) Vol. 65, Supp. [2], Sp. iss. SI, pp. 199-216. ISSN: 0906-4710.
Title	Long-term trends of pesticides in Norwegian agricultural streams and potential future challenges in northern climate
Publication Year	2015
Accession Number	2015:740666 SCISEARCH
Reliable with restrictions	Reliable with restrictions

Assessment and conclusion
The article evaluates data from Norwegian monitoring programs for pesticides to identify trends and future challenges for the Norwegian agriculture. For glyphosate, deficiencies in the monitoring methods were reported and only few information on the active ingredient is reported. Maximum glyphosate concentration of 4 µg/L.
The article is considered reliable with restrictions.

Edition No.: M-629321-01-1

Author	Szekacs, Andras (Reprint) Szekacs, Andras (Reprint); Moertl, Maria; Darvas, Bela
Source	JOURNAL OF CHEMISTRY, (2015) . ISSN: 2090-9063.
Title	Monitoring Pesticide Residues in Surface and Ground Water in Hungary: Surveys in 1990-2015
Publication Year	2015
Accession Number	2015:1470126 SCISEARCH
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports monitoring results for pesticide residues in surface and groundwater in Hungary. For Glyphosate a specific analytical method was used as with the methods used for other substances, no reliable LOD's were achieved. Only limited information on the results for glyphosate were reported. A maximum glyphosate concentration of 1 µg/L was reported.
The article is considered reliable with restrictions.

Edition No.: M-812437-01-1

Author	Tang Ting Boenne Wesley; Desmet Nele; Bronders Jan Seuntjens Piet van Griensven Ann
Source	The Science of the total environment, (2015 Jun 01) Vol. 517, pp. 207-14. Electronic Publication Date: 27 Feb 2015 Journal code: 0330500. E-ISSN: 1879-1026. L-ISSN: 0048-9697.
Title	Quantification and characterization of glyphosate use and loss in a residential area.
Publication Year	2015
Accession Number	2015598194 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes a modelling exercise to quantify and characterize the loss of glyphosate in a residential area to surface waters in Belgium. Overall, less than 0.5 % of applied glyphosate was recovered from the storm drain outflow. Maximum detected concentrations were 6.1 µg/L and 5.8 µg/L for glyphosate and AMPA, respectively. The authors concluded that measured concentrations and percentage loss rates could be attributed partially to the strong sorption capacity of glyphosate and low runoff potential in the study area.

The article is considered reliable.

Edition No.: M-523781-01-1

Author	Gasperi, J.; Sebastian, C.; Ruban, V.; Delamain, M.; Percot, S.; Wiest, L.; Mirande, C.; Caupos, E.; Demare, D.; et al.
Source	Environmental Science and Pollution Research, (2014) Vol. 21, No. 8, pp. 5267-5281. CODEN: ESPLEC. ISSN: 0944-1344.
Title	Micropollutants in urban stormwater: occurrence, concentrations, and atmospheric contributions for a wide range of contaminants in three French catchments
Publication Year	2014
Accession Number	2014:160593 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports the results from a monitoring exercise for micorpollutants in total atmospheric fallout (TAF) and stormwater of three French urban catchment areas. Occurrence of glyphosate and AMPA (in percent) were reported in TAF and stormwater. Among other pollutants, the concentrations of glyphosate and AMPA, expressed as mean ± SD, Q20 and Q80 were also reported. The results provide a comprehensive overview on the occurrence of glyphosate and AMPA in the stormwater of urban areas. However, the focus is not on agricultural areas.
The article is considered reliable with restrictions.

Edition No.: M-689205-01-1

Author	Maillard Elodie Imfeld Gwenael
Source	Environmental science & technology, (2014) Vol. 48, No. 15, pp. 8603-11. Electronic Publication Date: 17 Jul 2014 Journal code: 0213155. E-ISSN: 1520-5851. L-ISSN: 0013-936X.
Title	Pesticide mass budget in a stormwater wetland.
Publication Year	2014
Accession Number	2014904449 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article reports the pesticide loss and input in a stormwater wetland in an agricultural region in France. Several pesticides were analyzed, among them glyphosate and AMPA. Analytical methods were poorly described in the article but were provided in the supporting information. Mostly dissolved molecules, such as AMPA or fludioxonil, were moderately transported and less retained during the spring and late summer. Plant roots and fine sediments (50 and 250 μm) were the primary contributors to the retention of glyphosate, AMPA. AMPA accumulation in the fine sediments in late summer raises the issue of the ecotoxicological risk posed by the accumulation and the release of poorly described degradation products from wetland systems.

The article is considered reliable with restrictions.

Edition No.: M-812409-01-1

Author	Ramwell Carmel T Kah Melanie; Johnson Paul D
Source	Pest management science, (2014 Dec) Vol. 70, No. 12, pp. 1823-30. Electronic Publication Date: 20 Mar 2014 Journal code: 100898744. E-ISSN: 1526-4998. L-ISSN: 1526-498X.
Title	Contribution of household herbicide usage to glyphosate and its degradate aminomethylphosphonic acid in surface water drains.
Publication Year	2014
Accession Number	2014345827 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes the contribution of the household usage of glyphosate to concentrations of the active and AMPA in surface water drains. The set-up of the experiment excluded agricultural use. The sample site was an urban residential area in the UK. Overall, less than 0.6 % of applied glyphosate was recovered from the storm drain outflow. Maximum detected concentrations were 8.99 µg/L and 1.15 µg/L for glyphosate and AMPA, respectively.

Some information missing, e.g. sample storage.

The article is considered reliable with restrictions.

Edition No.: M-467954-01-1

Author	Daouk Silwan Grandjean Dominique; Chevre Nathalie; De Alencastro Luiz F; Pfeifer Hans-Rudolf
Source	Journal of environmental science and health. Part. B, Pesticides, food contaminants, and agricultural wastes, (2013) Vol. 48, No. 9, pp. 717-24. Journal code: 7607167. E-ISSN: 1532-4109. L-ISSN: 0360-1234.
Title	The herbicide glyphosate and its metabolite AMPA in the Lavaux vineyard area, Western Switzerland: proof of widespread export to surface waters. Part I: method validation in different water matrices.
Publication Year	2013
Accession Number	2013653313 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The main focus of the article is the validation of an analytical method in different water matrices. The measured values for glyphosate and AMPA from natural sites can be used for monitoring purposes. They represent a vineyard area in Switzerland.
The article is considered reliable.

Edition No.: M-812398-01-1

Author	Houtman, Corine J.; ten Broek, Rob; de Jong, Kevin; Pieterse, Bart; Kroesbergen, Jan
Source	Environmental Toxicology and Chemistry, (2013) Vol. 32, No. 11, pp. 2449-2459. CODEN: ETOCDK. ISSN: 0730-7268.
Title	A multicomponent snapshot of pharmaceuticals and pesticides in the river Meuse basin
Publication Year	2013
Accession Number	2013:445185 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the results of a monitoring exercise at the river Meuse in the Netherlands, where concentrations of 29 pharmaceuticals and 19 pesticides were reported from a multisite sampling campaign to evaluate the status of the Meuse. Glyphosate concentrations in the range of 0.02 to 0.21 µg/L and AMPA concentrations between 0.38 and 2.28 µg/L were reported.
The article is considered reliable.

Edition No.: M-812174-01-1

Author	Imfeld Gwenael Lefrancq Marie; Maillard Elodie; Payraudeau Sylvain
Source	Chemosphere, (2013 Jan) Vol. 90, No. 4, pp. 1333-9. Electronic Publication Date: 23 May 2012 Journal code: 0320657. E-ISSN: 1879-1298. L-ISSN: 0045-6535.
Title	Transport and attenuation of dissolved glyphosate and AMPA in a stormwater wetland.
Publication Year	2013
Accession Number	2012664913 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article reports concentration measurements for glyphosate and AMPA residues in an artificial stormwater wetland in France receiving runoff from a vineyard catchment with respect to the hydrological and hydrochemical conditions. Specific analytical methods were used and the limits of quantification were stated. The maximum glyphosate concentration entering the wetland was 150 µg/L. However, the maximum AMPA concentration was 19 µg/L.

The article is considered reliable with restrictions.

Edition No.: M-689196-01-1

Author	Vialle C Sablayrolles C; Silvestre J; Monier L; Jacob S; Huau M-C; Montrejaud-Vignoles M
Source	Journal of environmental management, (2013 May 15) Vol. 120, pp. 48-54. Electronic Publication Date: 15 Mar 2013 Journal code: 0401664. E-ISSN: 1095-8630. L-ISSN: 0301-4797.
Title	Pesticides in roof runoff: study of a rural site and a suburban site.
Publication Year	2013
Accession Number	2013466356 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article reports the concentrations of glyphosate and AMPA among some other hundreds of substances in the roof runoff from two experimental sites in France, one in a rural area, the other one in a suburban area. At the rural site, two groups of compounds associated with two different types of agriculture, vineyard and crops, were distinguished. The most frequently detected compound was glyphosate (83 %) which is the most commonly used herbicide in French vineyards. At the suburban site, quantified compounds were linked to agriculture rather than urban practices. The measured maximum concentrations of glyphosate and AMPA were 6 µg/L and 0.9 µg/L, respectively.

The article is considered reliable with restrictions.

Edition No.: M-812357-01-1

Author	Botta Fabrizio Fauchon Nils; Blanchoud Helene; Chevreuil Marc; Guery Benedicte
Source	Chemosphere, (2012 Jan) Vol. 86, No. 2, pp. 166-76. Electronic Publication Date: 9 Nov 2011 Journal code: 0320657. E-ISSN: 1879-1298. L-ISSN: 0045-6535.
Title	Phyt'Eaux Cites: application and validation of a programme to reduce surface water contamination with urban pesticides.
Publication Year	2012
Accession Number	2012027414 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes monitoring data (surface water) for glyphosate among other pesticides for an urban area in France. No agricultural area is considered. Glyphosate and AMPA concentrations are presented as Figures. The maximum recorded concentration of AMPA was 5.1 µg/L.
The article is considered reliable with restrictions.

Edition No.: M-812358-01-1

Author	Coupe Richard H Kalkhoff Stephen J; Capel Paul D; Gregoire Caroline
Source	Pest management science, (2012 Jan) Vol. 68, No. 1, pp. 16-30. Electronic Publication Date: 16 Jun 2011 Journal code: 100898744. E-ISSN: 1526-4998. L-ISSN: 1526-498X.
Title	Fate and transport of glyphosate and aminomethylphosphonic acid in surface waters of agricultural basins.
Publication Year	2012
Accession Number	2012090382 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article reports concentration measurements for glyphosate and AMPA residues in stream waters in USA and France. Specific analytical method were used and the limits of reporting were stated. The watersheds most at risk for the offsite transport of glyphosate are those with high application rates, rainfall that results in overland runoff and a flow route that does not include transport through soil. For the French catchment, only runoff events with volumes greater than 8 m3 were monitored between March and October. The article is considered reliable with restrictions.

Edition No.: M-813170-01-1

Author	Petersen Jens Grant Ruth; Larsen Soren E; Blicher-Mathiesen Gitte
Source	Journal of environmental monitoring : JEM, (2012 Dec) Vol. 14, No. 12, pp. 3284-94. Electronic Publication Date: 15 Nov 2012 Journal code: 100968688. E-ISSN: 1464-0333. L-ISSN: 1464-0325.
Title	Sampling of herbicides in streams during flood events.
Publication Year	2012
Accession Number	2013134175 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes an experiment in a Danish agricultural area, where glyphosate concentrations were measured during stream flood events. The development of concentrations levels after precipitation events were investigated. Different analytical methods were described. Maximum concentration of 2.8 µg/L for glyphosate and 0.54 µg/L for AMPA.
The article is considered reliable with restrictions.

Edition No.: M-812377-01-1

Author	Zgheib, Sally; Moilleron, Regis; Chebbo, Ghassan
Source	Water Research, (2012) Vol. 46, No. 20, pp. 6683-6692. CODEN: WATRAG. ISSN: 0043-1354.
Title	Priority pollutants in urban stormwater: Part 1 - Case of separate storm sewers
Publication Year	2012
Accession Number	2012:526591 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reports the contamination of stormwater with organic and mineral pollutants in the urban region of Paris. Among other substances, glyphosate and AMPA were measured and identified. The detected concentrations derive from atmospheric deposition and surface runoff from the urban environment, i.e. agricultural uses are not in the focus. Maximum glyphosate concentration of 232 µg/L in water (dissolved and particulate phases) and 8.3 µg/g dw (particulate phase). Maximum AMPA concentrations of 9.37 µg/L in water (dissolved and particulate phases) and 4 µg/g dw (particulate phase).
The article is considered reliable with restrictions.

Edition No.: M-813139-01-1

Author	Birch H Mikkelsen P S; Jensen J K; Lutzhoft H-C Holten
Source	Water science and technology : a journal of the International Association on Water Pollution Research, (2011) Vol. 64, No. 2, pp. 485-93. Journal code: 9879497. ISSN: 0273-1223. L-ISSN: 0273-1223.
Title	Micropollutants in stormwater runoff and combined sewer overflow in the Copenhagen area, Denmark.
Publication Year	2011
Accession Number	2012009303 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a monitoring experiment considering storm water from different catchments in the Copenhagen area. Glyphosate and AMPA were measured in the study, and the catchments are classified as mainly urban.
The article is considered reliable with restrictions.

Edition No.: M-812375-01-1

Author	Lamprea, K; Ruban, V
Source	Urban Water Journal [Urban Water J.]. Vol. 8, no. 4, pp. 219-231. 2011. ISSN: 1573-062X E-ISSN: 1744-9006 DOI: 10.1080/1573062X.2011.596211 Published by: Taylor & Francis Group Ltd., 2 Park Square Oxford OX14 4RN United Kingdom URL (Document): http://www
Title	Pollutant concentrations and fluxes in both stormwater and wastewater at the outlet of two urban watersheds in Nantes (France)
Publication Year	2011
Accession Number	2012:45717 PQSCITECH
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes a monitoring campaign in an urban area in the region of Nantes / France. Among others, glyphosate is measured. However, agricultural land use does not contribute significantly to the measured concentrations as the study area is described as an urban area. Median stormwater concentrations for glyphosate varied from 0.2 µg/L in dry weather, to 3.3 µg/L in wet weather (<0.1 and 0.4 µg/L for AMPA). In wastewater, glyphosate was not detected during dry weather (and AMPA could not be determined because of interference), while during wet weather median glyphosate concentrations reached 49 µg/L and AMPA 2 µg/L. Hence, urban use of glyphosate can generate significant residues in both stormwater and wastewater.

The article is considered reliable with restrictions.

Edition No.: M-812353-01-1

Author	Litz N T Weigert A; Krause B; Heise S; Grutzmacher G
Source	Water research, (2011 May) Vol. 45, No. 10, pp. 3047-54. Electronic Publication Date: 8 Mar 2011 Journal code: 0105072. E-ISSN: 1879-2448. L-ISSN: 0043-1354.
Title	Comparative studies on the retardation and reduction of glyphosate during subsurface passage.
Publication Year	2011
Accession Number	2011469229 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes experiments on subsurface passage of river water using so-called enclosures and semi-technical scale vertical slow sand filters (SSFs) to investigate the behavior of glyphosate and AMPA during bank filtration for drinking water supply. The filter experiments were supported by batch adsorption and degradation experiments with the filter material. Overall, the results showed that saturated subsurface passage has the potential to efficiently attenuate glyphosate, with aerobic conditions, long travel times and the presence of riparian boundary buffer strips. The main filter experiments and the analytical methods are well described and reported with sufficient details.
The article is considered reliable.

Edition No.: M-468255-01-1

Author	Maillard Elodie Payraudeau Sylvain; Faivre Etienne; Gregoire Caroline; Gangloff Sophie; Imfeld Gwenael
Source	The Science of the total environment, (2011 May 01) Vol. 409, No. 11, pp. 2317-24. Electronic Publication Date: 24 Feb 2011 Journal code: 0330500. E-ISSN: 1879-1026. L-ISSN: 0048-9697.
Title	Removal of pesticide mixtures in a stormwater wetland collecting runoff from a vineyard catchment.
Publication Year	2011
Accession Number	2011421107 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a runoff experiment in a vineyard of the Alsatian area in France. The results demonstrate that storm water wetlands can efficiently remove pesticide mixtures in agricultural runoff during critical periods of pesticide application, although fluctuations in the runoff regime and hydrochemical characteristics can affect the removal rates of individual pesticides. Maximum concentrations of glyphosate and its main metabolite AMPA measured at the inlet of the catchment were 15 µg/L and 21 µg/L, respectively.
The article is considered reliable.

Edition No.: M-813133-01-1

Author	Meyer, Berenike; Pailler, Jean-Yannick; Guignard, Cedric; Hoffmann, Lucien; Krein, Andreas
Source	Environmental Monitoring and Assessment, (2011) Vol. 180, No. 1-4, pp. 127-146. CODEN: EMASDH. ISSN: 0167-6369.
Title	Concentrations of dissolved herbicides and pharmaceuticals in a small river in Luxembourg
Publication Year	2011
Accession Number	2011:317819 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a monitoring study in an agricultural area in Luxembourg. The study design and the analytical methods are well described. The highest concentration of glyphosate was 6.22 µg/L and for AMPA was 1.118 µg/L.
The article is considered reliable.

Edition No.: M-467894-01-1

Author	Gregoire, C.; Payraudeau, S.; Domange, N. Editor(s): Chiron, S.
Source	International Journal of Environmental Analytical Chemistry (2010), Volume 90, Number 3/6, pp. 406-420, 39 refs. ISSN: 0306-7319 DOI: 10.1080/03067310903131230 Published by: Taylor & Francis, Abingdon Conference: Proceedings of the 5th European Conference
Title	Use and fate of 17 pesticides applied on a vineyard catchment.
Publication Year	2010
Accession Number	2010:134371 CABA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a monitoring study in a French vineyard catchment where glyphosate and AMPA among other pesticides were measured at the outlet flow of the catchment in water only observed during rainfall runoff events. Information on pesticide application amounts are provided as well as mean and max values of the measured concentrations on a yearly basis. The measured maximum concentration of glyphosate was 86 µg/L. Also, the measured maximum concentration of AMPA was 44 µg/L.
The article is considered reliable.

Edition No.: M-812167-01-1

Author	Hanke Irene Wittmer Irene; Bischofberger Simone; Stamm Christian; Singer Heinz
Source	Chemosphere, (2010 Sep) Vol. 81, No. 3, pp. 422-9. Electronic Publication Date: 8 Aug 2010 Journal code: 0320657. E-ISSN: 1879-1298. L-ISSN: 0045-6535.
Title	Relevance of urban glyphosate use for surface water quality.
Publication Year	2010
Accession Number	2010811196 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes a monitoring experiment in Switzerland covering a catchment with urban and agricultural land use. Glyphosate and its metabolite AMPA were analyzed. A comparison between the contribution of agricultural use and urban use to the overall load was conducted. Due to a specific definition of sub-catchment areas and their evaluation, a specific conclusion for the agricultural area can be given. It was clear that the majority of the total glyphosate load originated from urban areas. Analytical approaches were sufficiently described.
The article is considered reliable.

Edition No.: M-812151-01-1

Author	Malaguerra, Flavio [Reprint Author]; Albrechtsen, Hans-Jorgen; Thorling, Laerke; Binning, Philip John
Source	Science of the Total Environment, (JAN 1 2012) Vol. 414, pp. 433-444. http://www.journals.elsevier.com/science-of-the-total-environment/#description. CODEN: STENDL. ISSN: 0048-9697. E-ISSN: 1879-1026.
Title	Pesticides in water supply wells in Zealand, Denmark: A statistical analysis.
Publication Year	2012
Accession Number	2012:287723 BIOSIS
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes the statistical correlation of the occurrence of some pesticides, incl. glyphosate in groundwater wells with different characteristics of the wells (e.g. geology, geographic information, depth etc.). No measured values are reported.

Glyphosate and its metabolite AMPA are the most common compounds found in Danish streams at concentrations over 0.1 µg/L, with 26.7 % and 38.2 % respectively of samples in Danish streams recording such high concentrations (despite the lower number of samples for these two substances). Infiltration of surface runoff proposed.

The article is considered reliable with restrictions.

Edition No.: M-812154-01-1

Author	Sabatier Pierre; Poulenard Jerome; Fanget Bernard; Develle Anne-Lise; Ployon Estelle; Pignol Cecile; Arnaud Fabien Reyss Jean-Louis Wilhelm Bruno Naffrechoux Emmanuel Dorioz Jean-Marcel; Montuelle Bernard
Source	Proceedings of the National Academy of Sciences of the United States of America, (2014 Nov 04) Vol. 111, No. 44, pp. 15647-52. Electronic Publication Date: 13 Oct 2014 Journal code: 7505876. E-ISSN: 1091-6490. L-ISSN: 0027-8424. Report No.: NLM-PMC422612
Title	Long-term relationships among pesticide applications, mobility, and soil erosion in a vineyard watershed.
Publication Year	2014
Accession Number	2015201090 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article evaluates the long term relationship among pesticide applications, mobility and soil erosion in a French vineyard watershed. The sediment of an adjacent lake was investigated and compared with available information on historical usage of pesticides. It is postulated, from increasing levels of AMPA in the sediment core post-1990, that the increasing use of glyphosate from the early 1990s led to the remobilization of banned remnant pesticides (e.g. DDT) from vineyard soils.
The article is considered reliable.

Edition No.: M-813336-01-1

Author	Ravier, Sylvain; Desert, Marine; Gille, Gregory; Armengaud, Alexandre; Wortham, Henri; Quivet, Etienne [Reprint Author]
Source	Atmospheric Environment, (MAY 1 2019) Vol. 204, pp. 102-109. https://www.journals.elsevier.com/atmospheric-environment/. ISSN: 1352-2310. E-ISSN: 1873-2844.
Title	Monitoring of Glyphosate, Glufosinate-ammonium, and (Aminomethyl) phosphonic acid in ambient air of Provence-Alpes-Cote-d'Azur Region, France.
Publication Year	2019
Accession Number	2019:340128 BIOSIS
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the results of monitoring glyphosate and AMPA in the air of 4 different sites in the southeast of France. Maximum concentration of glyphosate measured at 1.04 ng/m^3
The article is considered reliable.

Edition No.: M-812462-01-1

Author	Hamann, Enrico; Stuyfzand, Pieter J.; Greskowiak, Janek; Timmer, Harrie; Massmann, Gudrun
Source	Science of the Total Environment, (2016) Vol. 545-546, pp. 629-640. CODEN: STENDL. ISSN: 0048-9697.
Title	The fate of organic micropollutants during long-term/long-distance river bank filtration
Publication Year	2016
Accession Number	2016:81168 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a modelling approach to describe long-term/long-distance river bank filtration for 29 compounds including AMPA. There are no new experimental data generated but the modeling approach gives relevant and reliable information on the behavior of AMPA at drinking water abstraction points.
The article is considered reliable.

Edition No.: M-812405-01-1

Author	Hedegaard Mathilde J Albrechtsen Hans-Jorgen
Source	Water research, (2014 Jan 01) Vol. 48, pp. 71-81. Electronic Publication Date: 25 Sep 2013 Journal code: 0105072. E-ISSN: 1879-2448. L-ISSN: 0043-1354.
Title	Microbial pesticide removal in rapid sand filters for drinking water treatment--potential and kinetics.
Publication Year	2014
Accession Number	2014039406 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The article describes experiments on the removal potential of glyphosate in rapid sand filters at Danish waterworks. Under the experimental conditions, glyphosate decreased to 7 – 14 % of initial amounts after 13 days (complete mineralisation); indicating that glyphosate was intrinsically degradable under these conditions (although unlikely to be degraded significantly *in situ*). The experiments are well described. However, no details on analytical methods are given. Further, sampling times and individual results are only reported for bentazone in graphical plots.

The article is considered reliable with restrictions.

Edition No.: M-813190-01-1

Author	Joensson, Joergen [Reprint Author]; Camm, Rob; Hall, Tom
Source	Journal of Water Supply Research and Technology - AQUA, (2013) Vol. 62, No. 7, pp. 395-408. CODEN: AQUAAA. ISSN: 0003-7214. E-ISSN: 1365-2087.
Title	Removal and degradation of glyphosate in water treatment: a review.
Publication Year	2013
Accession Number	2013:773177 BIOSIS
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes different methods used in drinking water treatment plants with regard to the degradation of glyphosate and AMPA, and presents a useful summary of removal efficiencies for glyphosate and AMPA.
The article is considered reliable.

Edition No.: M-813188-01-1

Author	Malaguerra, Flavio; Albrechtsen, Hans-Jorgen; Binning, Philip John
Source	Journal of hydrology (2013), Volume 476, pp. 321-331 ISSN: 0022-1694 Published by: Elsevier B.V. Source Note: 2013 Jan. 7, v. 476
Title	Assessment of the contamination of drinking water supply wells by pesticides from surface water resources using a finite element reactive transport model and global sensitivity analysis techniques
Publication Year	2013
Accession Number	2013:46443 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article reflects a computation model simulation for the contamination of drinking water wells with glyphosate and AMPA via filtration from surface waters. Generalized soil parameters were considered that reflect European agricultural soil characteristics. The derived results represents modelling results, no measured values.
The article is considered reliable with restrictions.

Edition No.: M-813156-01-1

Author	Ruel, S. Martin; Choubert, J.-M.; Budzinski, H.; Miege, C.; Esperanza, M.; Coquery, M.
Source	Water Science and Technology, (2012) Vol. 65, No. 7, pp. 1179-1189. CODEN: WSTED4. ISSN: 0273-1223.
Title	Occurrence and fate of relevant substances in wastewater treatment plants regarding Water Framework Directive and future legislations
Publication Year	2012
Accession Number	2012:255628 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the occurrence of glyphosate and AMPA among other substances in different wastewater treatment plants in France. The removal rate for glyphosate and AMPA observed in low load activated sludge process (data from five waste water treatment plants) was <30 %.
The analytical methods are poorly described.

The article is considered reliable with restrictions.

Edition No.: M-813136-01-1

Author	Ruel, S. Martin [Reprint Author]; Choubert, J. M.; Esperanza, M.; Miege, C.; Navalon Madrigal, P.; Budzinski, H.; Le Menach, K.; Lazarova, V.; Coquery, M.
Source	Water Science and Technology, (2011) Vol. 63, No. 11, pp. 2486-2497. CODEN: WSTED4. ISSN: 0273-1223.
Title	On-site evaluation of the removal of 100 micro-pollutants through advanced wastewater treatment processes for reuse applications.
Publication Year	2011
Accession Number	2011:471727 BIOSIS
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the efficiency of different wastewater treatment processes to remove glyphosate and AMPA among other substances from wastewater for reuse application. Different processes are described and their specific efficiency is reported. Removal rates for glyphosate and AMPA were: 30 – 70 % for glyphosate and AMPA for sand filtration, <30 % for AMPA for reverse osmosis and ozone treatment, but >70 % for glyphosate for reverse osmosis and ozone treatment; >70 % for both glyphosate and AMPA for activated carbon filtration.
The article is considered reliable.

Edition No.: M-509807-01-1

Author	Kegel F Schoonenberg Rietman B M; Verliefde A R D
Source	Water science and technology : a journal of the International Association on Water Pollution Research, (2010) Vol. 61, No. 10, pp. 2603-10. Journal code: 9879497. ISSN: 0273-1223. L-ISSN: 0273-1223.
Title	Reverse osmosis followed by activated carbon filtration for efficient removal of organic micropollutants from river bank filtrate.
Publication Year	2010
Accession Number	2010322115 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The study describes the removal of glyphosate among other substances from drinking water by reverse osmosis followed by activated carbon filtration. The substance properties and analytical methods are insufficiently described. The examined method focus on conservative filtration methods, no degradation products or processes are described.
The study is therefore classified as reliable with restrictions.

Edition No.: M-812345-01-1

Author	Assalin Marcia R De Moraes Sandra G; Queiroz Sonia C N; Ferracini Vera L; Duran Nelson
Source	Journal of environmental science and health. Part. B, Pesticides, food contaminants, and agricultural wastes, (2010 Jan) Vol. 45, No. 1, pp. 89-94. Journal code: 7607167. E-ISSN: 1532-4109. L-ISSN: 0360-1234.
Title	Studies on degradation of glyphosate by several oxidative chemical processes: ozonation, photolysis and heterogeneous photocatalysis.
Publication Year	2010
Accession Number	2010261248 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the removal of glyphosate by ozonation and photocatalysis (Ti/UV) process in water. The results are mainly shown as graphical plots. Thus, insufficient details were reported to evaluate the validity of the rate constants reported.
The article is considered reliable with restrictions.

Edition No.: M-813138-01-1

Author	Boucherie, C.; Lecarpentier, C.; Fauchon, N.; Djafer, M.; Heim, V.
Source	Water Science and Technology: Water Supply (2010), Volume 10, Number 5, pp. 860-868, 20 refs. ISSN: 1606-9749 DOI: 10.2166/ws.2010.837 Published by: IWA Publishing, London URL (Availability): http://www.iwaponline.com/ws/01005/0860/010050860.p df
Title	"Ozone" and "GAC filtration" synergy for removal of emerging micropollutants in a drinking water treatment plant?
Publication Year	2010
Accession Number	2011:61445 CABA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the removal of glyphosate and AMPA among other substances from spiked drinking water with a combined ozonation – deozonation - filtration approach. Glyphosate was found to be very rapidly degraded by ozone treatment (>91 %, levels reduced to <0.1 µg/L) and AMPA was rapidly removed (>88 %, levels reduced to <0.1 µg/L); hence, the ozone treatment required to deliver disinfection targets was also effective in removing glyphosate and AMPA to levels below 0.1 µg/L. However, no information about potential break-down products were provided.
The article is considered reliable with restrictions.

Edition No.: M-812165-01-1

Author	Manassero A Passalia C; Negro A C; Cassano A E; Zalazar C S
Source	Water research, (2010 Jul) Vol. 44, No. 13, pp. 3875-82. Journal code: 0105072. E-ISSN: 1879-2448. L-ISSN: 0043-1354.
Title	Glyphosate degradation in water employing the H2O2/UVC process.
Publication Year	2010
Accession Number	2010686791 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes the degradation of glyphosate under H2O2/UVC processes and the generation of breakdown products. The experiment is well described. A degradation pathway is proposed.
The article is considered reliable.

Edition No.: M-813217-01-1

Author	Rasmussen, Signe B.; Abrahamsen, Per; Nielsen, Marie H.; Holm, Peter E.; Hansen, Soren
Source	Vadose Zone Journal (1 Nov 2015) Volume 14, Number 11, 15 p., 68 refs. DOI: 10.2136/vzj2014.11.0164 Published by: Soil Science Society of America,
Title	Effects of single rainfall events on leaching of glyphosate and bentazone on two different soil types, using the DAISY model
Publication Year	2015
Accession Number	2015047539 ESBIOBASE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes a modelling assessment for the leaching of glyphosate through two different soil types. The effect of single rainfall events is analyzed. The modelling approach is not in line with current FOCUS guidelines.
Therefore, the article is classified as reliable with restrictions.

Title

公表文献調査報告書
グリホサート
別添資料 3
「区分 a」の文献に関する適合性及び信頼性判断理由

生活環境動植物及び家畜に対する毒性

(Summary of the literature data for Glyphosate: Appendix - Ecotoxicology)

Date

2022-06-27

Author(s)

バイエルクロップサイエンス株式会社

目次

Short summary of relevant and reliable articles from category a) with / without restrictions)
Edition No.: M-806130-01-1

Author	Rohr Jason R; Raffel Thomas R; Sessions Stanley K; Hudson Peter J
Source	Ecological applications : a publication of the Ecological Society of America, (2008 Oct) Vol. 18, No. 7, pp. 1743-53.
Title	Understanding the net effects of pesticides on amphibian trematode infections.
Publication Year	2008
Accession Number	2008647324
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
This study showed no significant effects of technical grade glyphosate (98%) on all the species involved in an amphibian trematode infection (i.e. the trematode Echinostoma trivolvis and its first and second intermediate hosts, the snail Planorbella trivolvis and tadpoles of the green frog Rana clamitans) when applied at 3.7 mg/L separatedly. A general NOEC of 3.7 mg/L can therefore be established. As some general methodological information is lacking and the tested individuals for all species were taken from natural sources with unknown previous history of chemical exposure/applications, which could make up the glyphosate effects, the article is considered reliable with restrictions.

Edition No.: M-813483-01-1

Author	Turhan Duygu Ozhan; Gungordu Abbas; Ozmen Murat
Source	Bulletin of environmental contamination and toxicology, (2020 Feb) Vol. 104, No. 2, pp. 173-179. Electronic Publication Date: 13 Jan 2020 Journal code: 0046021. E-ISSN: 1432-0800. L-ISSN: 0007-4861.
Title	Developmental and lethal effects of glyphosate and a glyphosate-based product on Xenopus laevis embryos and tadpoles.
Publication Year	2020
Accession Number	2021996422 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
Effects of pure glyphosate and a glyphosate-based product Roundup® Star (containing glyphosate in a form of a potassium salt and including 6% surfactant as ethoxylated alkylamine based, were evaluated comparatively using two embryonic development stages of the amphibian Xenopus laevis as model system. As the glyphosate-based product Roundup® Star is not the representative formulation for the European renewal of glyphosate, the summary only provides information for pure glyphosate.

However, this publication confirms a general trend that toxic effects caused by glyphosate-based products, compared to pure glyphosate, are increased mainly due to additives present in glyphosate formulations and that it may be a result of synergistic effects between glyphosate and adjuvant in the formulations.

In this study, no lethality >17 % or developmental effects (growth inhibition) were observed in embryos or tadpoles with pure glyphosate at any glyphosate concentration tested (282-500 mg/L for stage 8 embryos) and (250-403 mg/L stage 46 tadpoles)
In addition, no effect was observed with regards to enzymatic activity of stage 46 tadpoles at any glyphosate concentration tested (50-250 mg/L).

The article is classified as reliable with restrictions for the following reason : The specific purity of the test item was not reported. No OECD guidance has been followed. The American Society for Testing and Materials, Standard guide for conducting the Frog Embryo Teragonesis Assay-Xenopus (FETAX test), E1439-98 has been followed with some deviations to the recognised approach (see deviations above). The FETAX assay is a developmental toxicity screening test, which for the most part has been superseded by amphibian metamorphosis and developmental toxicity assays using Xenopus laevis (OECD 231 and OECD 241). Studies performed according to both of these recognised test guidelines were submitted with the Annex I dossier (M-CA Section 8.2.3/002 and M-CA Section 8.2.3/003). Whilst the FETAX assay is not directly recognised at the EU level, elements of the FETAX assay are considered in the conduct of the OECD 231 test guideline.
Control mortalities were not reported (only LC50 final results). Analytical verifications of the concentrations in the test medium were reported only before starting the test, but exposure medium was changed every 24 h to maintain the desired concentrations.

Edition No.: M-813596-01-1

Author	Diaz-Martin Ruben D; Carvajal-Peraza Ana Yanez-Rivera Beatriz Betancourt-Lozano Miguel
Source	Environmental toxicology and pharmacology, (2021 Jul 06) Vol. 87, pp. 103700. Electronic Publication Date: 6 Jul 2021 Journal code: 9612020. E-ISSN: 1872-7077. L-ISSN: 1382-6689.
Title	Short exposure to glyphosate induces locomotor, craniofacial, and bone disorders in zebrafish (Danio rerio) embryos.
Publication Year	2021
Accession Number	2024291712 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This article used the zebrafish model to assess the effects of early life glyphosate exposure on the development of cartilage and bone tissues and organismal responses. The evidence suggests functional alterations, including a reduction in the cardiac rate, significant changes in the spontaneous tail movement pattern, and defects in craniofacial development. These effects were concomitant with alterations in the level of the oestrogen receptor alpha osteopontin and bone sialoprotein. Embryos exposed to glyphosate presented spine deformities as adults. These developmental alterations are likely induced by changes in protein levels related to bone and cartilage formation.

This article is of importance for the assessment of the endocrine disrupting properties of glyphosate. It reports the acute and chronic effects on zebra fish. The study seems to have been well conducted and reports a regulatory relevant and reliable endpoint: 96 h NOEC = 1 mg/L (based on the effects on bone sialoprotein (BSPII) relative expression). The study is considered reliable with restrictions because it lacks of analytical verifications of the tested item in the test medium during the exposure phase. Temperature during the test is a bit high for the species tested.

Edition No.: M-812205-01-1

Author	Antunes Adriana Maria; Rocha Thiago Lopes; Pires Fernando Santiago; de Freitas Meire Alves; Leite Vanessa Rafaela Milhomem Cruz; Saboia-Morais Simone Maria Teixeira Rocha Thiago Lopes Arana Sarah Moreira Paulo Cesar
Source	Journal of applied toxicology : JAT, (2017 Sep) Vol. 37, No. 9, pp. 1098-1107. Electronic Publication Date: 20 Apr 2017 Journal code: 8109495. E-ISSN: 1099-1263. L-ISSN: 0260-437X.
Title	Gender-specific histopathological response in guppies Poecilia reticulata exposed to glyphosate or its metabolite aminomethylphosphonic acid.
Publication Year	2017
Accession Number	2018494263 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The acute 96 hour-LC50 values for male and female guppies P. reticulata after exposure to glyphosate were 68.78 mg/L and 70.87 mg/L, respectively. The acute 96 hour-LC50 values for AMPA for male and female guppies were 180 mg/L and 164.3 mg/L, respectively.

In the material and methods part some important is missing. No information on preparation of test solution and application is given. Source and composition of media are unclear. Furthermore, there was no analytical verification of test concentrations reported. The study is considered as reliable with restrictions.

Edition No.: M-806118-01-1

Author	Langiano Vivian Do Carmo; Martinez Claudia B R
Source	Comparative biochemistry and physiology. Toxicology and pharmacology : CBP, (2008 Mar) Vol. 147, No. 2, pp. 222-31. Electronic Publication Date: 26 Sep 2007
Title	Toxicity and effects of a glyphosate -based herbicide on the Neotropical fish Prochilodus lineatus.
Publication Year	2008
Accession Number	2007764583
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

In this article acute and sub-lethal endpoints for the neotropical fish Prochilodus lineatus after exposure to the glyphosate formulation Roundup® are reported. The determined 96 h LC50 of 13.69 mg/L is considered relevant for risk assessment. As the test concentrations were not analytically verified, no raw data are presented and no confidence intervals are given for the 96 h LC50, the article is considered as reliable with restrictions (NOTE: probably not relevant because of the formulation used).

Edition No.: M-803588-01-1

Author	Stehr, Carla M; Linbo, Tiffany L; Baldwin, David H; Scholz, Nathaniel L; Incardona, John P
Source	North American Journal of Fisheries Management [N. Am. J. Fish. Manage.]. Vol. 29, no. 4, pp. 975-984. Aug 2009. ISSN: 0275-5947 E-ISSN: 1548-8675 DOI: 10.1577/M08-173.1 Published by: American Fisheries Society, 5410 Grosvenor Ln. Bethesda MD 20814-2199 U
Title	Evaluating the Effects of Forestry Herbicides on Fish Development Using Rapid Phenotypic Screens
Publication Year	2009
Accession Number	2009:757121
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
In this article the developmental effects (anatomy, morphology, body length, touch response) of glyphosate on zebra fish embryos after 5 days of exposure were assessed. No significant effects were observed at the highest test concentration of 100 mg/L. As the test concentrations were not analytically verified and the raw data are not presented, the article is considered reliable with restrictions.

Edition No.: M-812512-01-1

Author	Forner-Piquer, Isabel; Faucherre, Adele; Byram, Julia; Blaquiere, Marine; de Bock, Frederic; Gamet-Payrastre, Laurence; Ellero-Simatos, Sandrine; Audinat, Etienne; Jopling, Chris; Marchi, Nicola
Source	Chemosphere, (2021) Vol. 267, pp. 128986. CODEN: CMSHAF. ISSN: 0045-6535.
Title	Differential impact of dose-range glyphosate on locomotor behavior, neuronal activity, glio-cerebrovascular structures, and transcript regulations in zebrafish larvae.
Publication Year	2021
Accession Number	2021:10368 TOXCENTER
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
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.

Edition No.: M-813607-01-1

Author	Le Du-Carree Jessy Boukhari Rania; Cabon Joelle; Louboutin Lenaig; Morin Thierry; Danion Morgane Cachot Jerome
Source	The Science of the total environment, (2021 Aug 04) Vol. 801, pp. 149462. Electronic Publication Date: 4 Aug 2021 Journal code: 0330500. E-ISSN: 1879-1026. L-ISSN: 0048-9697.
Title	Generational effects of a chronic exposure to a low environmentally relevant concentration of glyphosate on rainbow trout, Oncorhynchus mykiss.
Publication Year	2021
Accession Number	2024465369 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This study investigates the impact of an environmentally relevant concentration of glyphosate on a F2 generation issued from exposed generations F0 and F1. Trans, inter and multigenerational toxicity of 1 µg/L of the active substance was evaluated on early stages of development and juvenile rainbow trout (Oncorhynchus mykiss) using different molecular, biochemical, immuno hematologic, and biometric parameters, behaviour analysis, and a viral challenge. Reproductive parameters of generation F1 were not affected. However, developmental toxicity in generation F2 due to glyphosate alone or co formulated was observed with head size changes (e.g. head surface up to +10%), and metabolic disruptions (e.g. 35% reduction in cytochrome c oxidase). Therefore, LOEC = 1 µg/L.

The study is not considered fully reliable because although it presents analytical verifications of the tested item in the water in the exposure phase, it does not fully follow any agreed guidance and only one concentration was tested. Temperature of the test could have been a bit low for the tested species at some time points of the experiment.

Edition No.: M-812318-01-1

Author	Du-Carree Jessy Le Morin Thierry; Danion Morgane
Source	Aquatic toxicology (Amsterdam, Netherlands), (2021 Jan) Vol. 230, pp. 105687. Electronic Publication Date: 26 Nov 2020 Journal code: 8500246. E-ISSN: 1879-1514. L-ISSN: 0166-445X.
Title	Impact of chronic exposure of rainbow trout, Oncorhynchus mykiss, to low doses of glyphosate or glyphosate-based herbicides.
Publication Year	2021
Accession Number	2023322026 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
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.

Edition No.: M-813592-01-1

Author	Le Du-Carree Jessy Saliou Florian; Morin Thierry; Danion Morgane Cachot Jerome
Source	Aquatic toxicology (Amsterdam, Netherlands), (2021 Aug) Vol. 237, pp. 105894. Electronic Publication Date: 6 Jun 2021 Journal code: 8500246. E-ISSN: 1879-1514. L-ISSN: 0166-445X.
Title	Developmental effect of parental or direct chronic exposure to environmental concentration of glyphosate on the larvae of rainbow trout, Oncorhynchus mykiss.
Publication Year	2021
Accession Number	2024240744 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This study investigates the impact of parental and direct exposure to 1 µg/L of glyphosate using the active subtance alone or one of two Glyphosate-Based Herbicide formulations (i.e. Roundup Innovert® and Viaglif Jardin®) in the early developmental stages of rainbow trout. Three different modes of exposure on the F1 generation were studied: (1) intergenerational (i.e. fish only exposed through their parents); (2) direct (i.e. fish exposed only directly) and (3) multigenerational (i.e. fish both exposed intergenerationally and directly). The impact of chemical treatments on embryo -larval development (survival, biometry and malformations), swimming behaviour, biochemical markers. Chemical exposure did not affect the survival of F1 embryos or malformation rates. Direct exposure to the a.s. induced some biometric changes, such as reduction in head size (with a 10% decrease in head length), independently of co -formulants. Intergenerational exposure to the a.s. or the Roundup GBH increased swimming activity of the larvae, with increase of between 78 and 102% in travel speeds. Therefore, 1 generation LOEC = 1 µg/L.

The study is not considered fully reliable because although it presents analytical verifications of the tested item in the water in the exposure phase, it does not fully follow any agreed guidance and only one concentration was tested. Temperature of the test could have been a bit low for the tested species at some time points of the experiment.

Edition No.: M-812269-01-1

Author	de Brito Rodrigues Lais; Goncalves Costa Gessyca; Campos Valadares Marize Lundgren Tha Emanoela; da Silva Lucas Rafael; Cestari Marta Margarete de Oliveira Rhaul Morais Leme Daniela Koppe Grisolia Cesar de Oliveira Gisele Augusto Rodrigues
Source	Mutation research, (2019 Jun) Vol. 842, pp. 94-101. Electronic Publication Date: 4 May 2019 Journal code: 0400763. E-ISSN: 1873-135X. L-ISSN: 0027-5107.
Title	Impact of the glyphosate-based commercial herbicide, its components and its metabolite AMPA on non-target aquatic organisms.
Publication Year	2019
Accession Number	2021323372 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The acute toxicity of technical glyphosate and its metabolite aminomethylphosphonic acid (AMPA) to zebrafish embryos was investigated.

Glyphosate and AMPA caused no acute toxic effect (LC50-96 h > 100 mg/L) in zebrafish.

The study was stated to have been conducted according to OECD guideline 236, but there is no information on hatching rates in the treatment and control groups, so exposure of the embryo without a potential barrier function of the chorion cannot be confirmed.

Concerning the validity of the study, four of the six validity criteria from the test guideline are mentioned in the paper (fertilization rate of embryo batches used was >90%, survival in the negative control group was > 90%, temperature was maintained at 26 ±1ºC and dissolved oxygen was at an acceptable level 8ppm). There is no information presented on the performance of the positive control group (3, 4-dichloroaniline) and no information provided on the hatching rates in the negative control group at 96 hours, which for the control group should exceed 80%. As these information are not presented and the fact that there was no analytical verification of test concentrations reported, this study considered as reliable with restrictions.

Edition No.: M-813470-01-1

Author	Schweizer Mona; Triebskorn Rita; Kohler Heinz-R Brilisauer Klaus; Forchhammer Karl Triebskorn Rita
Source	PeerJ, (2019) Vol. 7, pp. e7094. Electronic Publication Date: 19 Jun 2019 Journal code: 101603425. ISSN: 2167-8359. L-ISSN: 2167-8359. Report No.: PMC-PMC6589083.
Title	How glyphosate and its associated acidity affect early development in zebrafish (Danio rerio).
Publication Year	2019
Accession Number	2021317895 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

For Zebrafish (*Danio rerio*) embryos acutely exposed to glyphosate at concentrations between 1.69 and 1690.7 mg glyphosate/L (10 µM to 10 mM) for 96 hours post fertilization (hpf) the LC_{10} and LC_{50} values (96 hpf) were calculated to be 65.1 mg a.s./L (385 µM) and 98.4 mg a.s./L (582 µM), respectively (in unbuffered glyphosate medium). Regarding heart rates the EC_{10} was 7.27 mg a.s./L (43 µM). Concerning hatching rate, 96 hpf -EC_{10} and EC_{50} values were 26.2 mg a.s./L (155 µM) and 37.9 (224 µM), respectively. For developmental delays at 24 hpf the EC10 was 21.3 mg a.s./L (126 µM). The test was conducted according to OECD 236 test guideline.

Concerning the validity criteria in the OECD 236, despite the stated > 80% mortality in the positive control (>30% required) there are no details presented to confirm the level of mortality. The fertilisation rate of the batch of eggs used was not reported. Finally, acute endpoints based on developmental delay and heart rate are not relevant to an EU level risk assessment for Annex I renewal purposes.

The test design is adequately described, however, there was no analytical verification of test concentrations reported. The study is considered as reliable with restrictions.

Edition No.: M-805378-01-1

Author	Pereira Joana L; Antunes Sara C; Castro Bruno B; Marques Catarina R; Goncalves Ana M M; Goncalves Fernando; Pereira Ruth
Source	Ecotoxicology (London, England), (2009 May) Vol. 18, No. 4, pp. 455-63. Electronic Publication Date: 10 Feb 2009
Title	Toxicity evaluation of three pesticides on non-target aquatic and soil organisms: commercial formulation versus active ingredient.
Publication Year	2009
Accession Number	2009246832
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

In this article, acute endpoints for Daphnia magna and the green algae Pseudokirchneriella subcapitata after exposure to the glyphosate formulation Spasor® or the active substance glyphosate are reported, i.e. 307 mg/L (> 2000 mg/L) for Daphnia magna and 71 mg/L (129 mg/L) for P. subcapitata. As the test concentrations were not analytically verified and no raw data are presented, the article is considered reliable with restrictions.

Edition No.: M-805373-01-1

Author	Bringolf Robert B; Cope W Gregory; Mosher Shad; Barnhart M Chris; Shea Damian
Source	Environmental toxicology and chemistry, (2007 Oct) Vol. 26, No. 10, pp. 2094-100.
Title	Acute and chronic toxicity of glyphosate compounds to glochidia and juveniles of Lampsilis siliquoidea (Unionidae).
Publication Year	2007
Accession Number	2007552815
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The article describes acute and chronic toxicity tests with different forms of glyphosate and different glyphosate formulations on juveniles and glochidia of the freshwater mussel Lampsilis siliquoidea. Acute 48 EC50 values for the different glyphosate forms (4.6 - 200 mg/L) and glyphosate formulations (2.9 - 148 mg/L) are reported, which are partially considered relevant for risk assessment. As no raw data are provided, the test doses used for the acute test are not reported and the analytical methods are not clearly described, the article is regarded reliable with restrictions.

Edition No.: M-812436-01-1

Author	Levine Steven L; Manson Philip von Merey Georg Minderhout Tui Sutton Peter
Source	Environmental toxicology and chemistry, (2015 Jun) Vol. 34, No. 6, pp. 1382-9. Electronic Publication Date: 17 Apr 2015 Journal code: 8308958. E-ISSN: 1552-8618. L-ISSN: 0730-7268.
Title	Aminomethylphosphonic acid has low chronic toxicity to Daphnia magna and Pimephales promelas.
Publication Year	2015
Accession Number	2015563523 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
Chronic toxicity tests of the glyphosate environmental metabolite aminomethylphosphonic acid (AMPA) were performed with fathead minnow (Pimephales promelas) and Daphnia magna.
During a 21-d exposure period under semi-static test conditions the effects on survival, growth, and reproduction of the cladoceran Daphnia magna were determined resulting in a no-observed-effect concentration (NOEC) of 15 mg AMPA/L. During a 33-d exposure period under continuous renewal test conditions the effects on time to hatch, hatching success, posthatch growth and survival of the fish Pimephales promelas were assessed resulting in an NOAEC of 12 mg AMPA/L, the highest tested concentration. Test methodology followed the procedure outlined in the OECD 210 test guideline for P. promelas. For the chronic test on Daphnia magna the OECD 211 guideline is mentioned in the full text.

The study is well documented and all relevant information, e.g. information on the test item, test design, application method and implementation of the study, is available. In addition, a chemical analysis of test solutions was performed. All information for evaluation of the study is given. The study is considered as reliable.

Available on the website: http://dx.doi.org/10.14719/pst.2021.8.2.1068

Author	Kaeoboon, Somruthai; Suksungworn, Rungcharn; Sanevas, Nuttha [Reprint Author]
Source	Plant Science Today, (2021) Vol. 8, No. 2, pp. 293-300. http://horizonepublishing.com/journals/index.php/PST/index. ISSN: 2348-1900. E-ISSN: 2348-1900.
Title	Toxicity response of Chlorella microalgae to glyphosate herbicide exposure based on biomass, pigment contents and photosynthetic efficiency.
Publication Year	2021
Accession Number	2021:778353 BIOSIS
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This article reports the effects of glyphosate at different concentrations (50 500 mg/L) on three Chlorella species including *Chlorella ellipsoidea*, *Chlorella sorokiniana* and *Chlorella vulgaris* in relation to the biomass, pigment contents and photosynthetic efficiency. The study seems to have been well conducted and reports regulatory relevant endpoints: 24 h acute EC50 = 449.34, 288.23 and 174.28 mg/L for *Chlorella vulgaris*, *Chlorella ellipsoidea* and *Chlorella sorokiniana*, respectively. Chronic endpoints at 72 h could also be calculated.

The study cannot be considered as fully reliable because it lacksc analytical verifications of the tested item in the test medium and the temperature during the tests and culture are higher than recommended for green algae. Purity of the test item is not given.

Edition No.: M-806102-01-1

Author	Vendrell E; Ferraz D Gomez De Barreda; Sabater C; Carrasco J M
Source	Bulletin of environmental contamination and toxicology, (2009 May) Vol. 82, No. 5, pp. 538-42. Electronic Publication Date: 6 Mar 2009
Title	Effect of glyphosate on growth of four freshwater species of phytoplankton: a microplate bioassay.
Publication Year	2009
Accession Number	2009214613
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
In this article the effect of technical glyphosate (97.5%) on the growth of four freshwater algae species was tested in a 72 hour exposure test. EC50 values based on area under the growth curve are reported, which ranged between 24.5 and 41.7 mg/L. As the test concentrations were not analytically verified and no raw data are presented, the article is considered reliable with restrictions.

Edition No.: M-813528-01-1

Author	Tajnaiova, Lucia ; Vurm, Radek ; Kholomyeva, Marina ; Kobera, Miroslav ; Koci, Vladimir
Source	Plants (14 Sep 2020), Volume 9, Number 9 ISSN: 2223-7747 Source Note: 20200914, v. 9, no. 9
Title	Determination of the Ecotoxicity of Herbicides Roundup® Classic Pro and Garlon New in Aquatic and Terrestrial Environments
Publication Year	2020
Accession Number	2021:11973 AGRICOLA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The study reports on endpoints with possible relevance to the EU-level risk assessment for aquatic organisms, specifically freshwater algae (*Desmodesmus subspicatus*) and aquatic plants (*Lemna minor*) for the glyphosate metabolite AMPA. For *D. subspicatus*, a regulatory relevant endpoint is reported (IC_{50} for inhibition of growth rate, usually described as ErC_{50}). For the *Lemna* test, no regulatory relevant endpoint was reported but the assessed parameters (growth rate, front area and chlorophyll content) could potentially serve as supporting information in a weight of evidence approach.
As the tests differed both in design as in the reported endpoints, assessments of reliability should be looked at separately.

Test with *D. subspicatus*: The report states that the test was conducted according to ISO 8692 with not further specified modifications. Furthermore, it is reported, that the test fulfilled the validity criteria laid down by OECD test guideline for freshwater algae. There are however important information missing from the report. Specifically, no data of the negative control are presented not even in the supplementary material. No raw data are provided so, the validity criteria could not be checked. Furthermore, the IC_{50} value was calculated without confidence intervals and no parameters to judge the fit of the curve used for calculating the IC_{50} are presented. The certainty of the level of protection can therefore not be fully assessed.

Test with *L. minor*: While relevant parameters were assessed (such as growth rate and front area), no regulatory relevant endpoints, such as ECx values, were calculated. No justifications are provided. Furthermore, control data are only presented for the parameters front area and chlorophyll content, and only in a graphical format. Due to the lack of raw data, no regulatory relevant endpoints can be calculated retroactively.

For both tests: The purity of the test material was not reported. Furthermore, exposure concentrations were not analytically verified. Especially for the *Lemna* test, which lasted 7 days without renewal of the test substance, actual exposure concentrations could vary significantly from the nominal concentrations.

Based on the above mentioned issues for both tests, the study can only be deemed reliable with restrictions.

Edition No.: M-469975-01-1

Author	Cedergreen, Nina; Kudsk, Per; Mathiassen, Solvejg K.; Streibig, Jens C.
Source	Pest Management Science (2007), 63(3), 282-295
Title	Combination effects of herbicides on plants and algae: do species and test systems matter?
Publication Year	2007
Accession Number	2007:262630
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
In this study, the toxicity of technical grade glyphosate (95%) on the terrestrail plants Tripleurospermum inodorum (ED50 = 18 ± 1 g a.s./ha) and Stellaria media (ED50 = 16 ± 3 g a.s./ha), the aquatic plant Lemna minor (EC50 = 17.2 ± 1.1 mg a.s./ha) and the alga Pseudokirchneriella subcapitata (EC50 = 55.1 ± 2.5 mg a.s./ha) was calculated. As no analytical verifications were conducted for any of the tests with either terrestrial or aquatic species, some important methodological details are insufficiently reported and no raw data are available to verify ED/EC50 values, the article is considered reliable with restrictions.

Edition No.: M-813594-01-1

Author	Mendes Evelyn Joslin; Malage Laura; Rocha Daiane Cristina; Kitamura Rafael Shinji Akiyama Gomes Sandra Maria Alvarenga Navarro-Silva Mario Antonio Gomes Marcelo Pedrosa
Source	Journal of hazardous materials, (20210905) Vol. 417, pp. 125694. Electronic Publication Date: 20 Mar 2021 Journal code: 9422688. E-ISSN: 1873-3336. L-ISSN: 0304-3894.
Title	Isolated and combined effects of glyphosate and its by-product aminomethylphosphonic acid on the physiology and water remediation capacity of Salvinia molesta.
Publication Year	2021
Accession Number	2024283670 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This study evaluates the isolated and combined effects of glyphosate and its by product aminomethylphosphonic acid (AMPA) on the aquatic macrophyte *Salvinia molesta*. Plants were exposed to environmentally relevant concentrations of glyphosate (0, 20, 40, 60, 80 and 100 µg/L) or AMPA (0, 10, 20, 30, 40 and 50 µg/L) for seven days. Then, based on the effective concentrations of glyphosate found to reduce photosynthetic rates by 10% (EC10) and 50% (EC50), the plants were exposed to combinations of 0, 16 and 63.5 µg glyphosate/L and 0, 5, 15, 25 µg AMPA/L. The EC10 and EC50 were lower for AMPA (6.1 µg/L and 28.4 µg/L, respectively) than for glyphosate (16 and 63.5 µg glyphosate/L, respectively). When occurring together, the deleterious effects of those chemicals to plants increased.

The study is considered not fully reliable because it is not possible to identify the number of plants tested for each treatment and because plants were collected from the field in Brazil with no record of previous pesticide exposure (although they were maintained in the lab for 60 days for depuration).

Edition No.: M-813609-01-1

Author	Vera Maria Solange Trinelli Maria Alcira
Source	Environmental pollution (Barking, Essex : 1987), (2021 Aug 18) Vol. 290, pp. 117998. Electronic Publication Date: 18 Aug 2021 Journal code: 8804476. E-ISSN: 1873-6424. L-ISSN: 0269-7491.
Title	First evaluation of the periphyton recovery after glyphosate exposure.
Publication Year	2021
Accession Number	2024482227 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This is a higher tier study for aquatic organisms with two glyphosate concentrations tested (0.4 and 4 mg/L) on aquatic microcosms. The study is structured in two phases: 7 days of exposure to treated water and 21 days of recovery in clean water (both of them under static conditions). It evaluates the potential of freshwater periphyton to recover from glyphosate exposure using microcosms under laboratory conditions. Dry weight, ash free dry weight, chlorophyll a, and periphyton abundances were analysed. The periphyton affected with the lowest concentration recovered most of the structural parameters within 7 days in clean water, but the taxonomic structure did not entirely recover towards the control structure. Periphyton exposed to 4 mg/L could not recover during 21 days in herbicide free water, reaching values almost four times higher in % of dead diatoms and four times lower in ash free dry weight concerning the control at the end of the study. Results suggest a long lasting effect of the herbicide due to the persistence within the community matrix even after translocating periphyton to decontaminated water. The study concludes that the exposure concentration modulates the recovery potential of impacted periphyton.

The study is considered reliable with restrictions. Analytical verifications of the tested item in the test medium were conducted at the beginning and the end of the exposure phase.

Edition No.: M-813115-01-1

Author	Daam Michiel A Moutinho Mariana F Espindola Evaldo L G Schiesari Luis
Source	Ecotoxicology (London, England), (2019 Jun 27) . Electronic Publication Date: 27 Jun 2019 Journal code: 9885956. E-ISSN: 1573-3017. L-ISSN: 0963-9292.
Title	Lethal toxicity of the herbicides acetochlor, ametryn, glyphosate and metribuzin to tropical frog larvae.
Publication Year	2019
Accession Number	2021318446 MEDLINE (EPUB AHEAD OF PRINT)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion
The study investigated the acute toxicity of glyphosate to larvae of *Physalaemus cuvieri* and *Hypsiboas pardalis.* The LC_{50} for *Physalaemus cuvieri* and *Hypsiboas pardali* was determined to be 115 mg a.s./L and 106 mg a.s./L, respectively.

The study was conducted according to portions of OECD 241. However, validity criteria were not reported. It is unknown if the larvae were exposed to any other chemicals as no analysis of watershed water was provided. There was no analytical verification of test concentrations reported. The study is considered as reliable with restrictions.

Edition No.: M-813499-01-1

Author	Odemer Richard; Alkassab Abdulrahim T; Frommberger Malte; Wernecke Anna; Wirtz Ina P; Pistorius Jens Bischoff Gabriela Odemer Franziska
Source	Insects, (2020 Sep 27) Vol. 11, No. 10. Electronic Publication Date: 27 Sep 2020 Journal code: 101574235. ISSN: 2075-4450. L-ISSN: 2075-4450. Report No.: PMC-PMC7600025.
Title	Chronic High Glyphosate Exposure Delays Individual Worker Bee (Apis mellifera L.) Development under Field Conditions.
Publication Year	2020
Accession Number	2023051041 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion

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.

Edition No.: M-813519-01-1

Author	von Merey, Georg; Akbar Mehrsheikh; Peter Sutton; Philip S Manson; Steven L Levine
Source	Environmental toxicology and chemistry (2016), pp. 2742-2752 ISSN: 0730-7268 Published by: John Wiley & Sons, Ltd Source Note: 2016 Nov., v. 35, no. 11
Title	Glyphosate and aminomethylphosphonic acid chronic risk assessment for soil biota
Publication Year	2016
Accession Number	2017:338828 AGRICOLA
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
The aim of the paper was to evaluate potential effects of Glyphosate, Glyphosate salt and AMPA on earthworm, soil mites, springtails and soil micro-organisms.
The studies have been conducted according to recognised guidelines and validity criteria were presented. Test substance information, test organism origin, study designs and toxicity effects were adequately described. The study is considered reliable.

Edition No.: M-813489-01-1

Author	Rogacz Diana; Rychter Piotr Lewkowski Jaroslaw Cal Dariusz
Source	Ecotoxicology and environmental safety, (2020 May) Vol. 194, pp. 110331. Electronic Publication Date: 5 Mar 2020 Journal code: 7805381. E-ISSN: 1090-2414. L-ISSN: 0147-6513.
Title	Ecotoxicological effects of new C-substituted derivatives of N-phosphonomethylglycine (glyphosate) and their preliminary evaluation towards herbicidal application in agriculture.
Publication Year	2020
Accession Number	2022208559 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
The study investigated the effects of glyphosate on the seedling emergence and growth of non-target terrestrial plants (oat and radish) based on OECD 208 guideline. Plants were exposed to glyphosate mixed into sandy soil at 5 concentrations between 100 and 100 mg a.s./kg of soil dry weight with 3 replicates each. There were 20 seeds of each plant species per test concentration sown into the soil. Evaluations were based on fresh mass, root length and shoot height of plants after 14 days of exposure.

The test design was adequately described, but the application of the test item into the soil is not specified. The seedling emergence was acceptable as recommended in the guideline (100 and 95 % in the control for oat and radish, respectively). However, the phytotoxic effects and the survival of the control plants during the study is not reported.
Reliable endpoints for the risk assessment of NTTPs can be obtained for glyphosate: EC50 value of 373.7 mg a.s./kg s.d.w. for oat based on shoot height and an EC50 value of 357.8 mg a.s./kg s.d.w. for radish based on shoot height.

The article is classified as reliable for NTTPs.

Edition No.: M-813610-01-1

Author	Goodman Rachel M Carter Edward Davis; Miller Debra L Miller Debra L
Source	Viruses, (2021 Jul 23) Vol. 13, No. 8. Electronic Publication Date: 23 Jul 2021 Journal code: 101509722. E-ISSN: 1999-4915. L-ISSN: 1999-4915. Report No.: PMC-PMC8402795.
Title	Influence of Herbicide Exposure and Ranavirus Infection on Growth and Survival of Juvenile Red-Eared Slider Turtles (Trachemys scripta elegans).
Publication Year	2021
Accession Number	2024505803 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

In this study, hatchling red eared slider turtles (Trachemys scripta elegans) were exposed to the formulated glyphosate herbicides Roundup ProMax® and Rodeo® to examine direct effects on growth and mortality. Turtles were exposed to herbicides via water bath during the first 3 weeks of a 5 week experiment. Exposure to a NOEC = 2 mg/L concentration of glyphosate (for both products) did not impact growth or survival time of hatchling turtles.

The study cannot be considered as fully reliable because it is uncertain whether and when the samples from the final herbicide solutions that were analysed to verify target concentrations, were taken from the experimental cages. In addition, the test items were not documented and only one concentration of each product was tested.hous

Edition No.: M-813578-01-1

Author	Gustinasari Kiki; Pandebesie Ellina S; Hermana Joni Slugocki Lukasz; Czerniawski Robert
Source	Toxicological research, (2021 Apr) Vol. 37, No. 2, pp. 197-207. Electronic Publication Date: 27 Jul 2020 Journal code: 101483324. ISSN: 1976-8257. L-ISSN: 1976-8257. Report No.: PMC-PMC8007680.
Title	Acute toxicity and morphology alterations of glyphosate-based herbicides to Daphnia magna and Cyclops vicinus.
Publication Year	2021
Accession Number	2023924338 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The study provides regulatory relevant endpoints, specifically the LC_{50} for *D. magna* and *C. vicinus* after 48-hours exposure. However, the study cannot be deemed fully reliable due to the following aspects: First, the exposure concentrations were not analytically verified. Furthermore, previous exposure of *C. vicinus* to contaminants cannot be excluded as they were collected from a river with unknown contamination history. In addition, the exposure medium was not specified (possibly distilled water, but the phrasing is ambiguous) and important info on the culturing conditions is missing (i.e. temperature, etc.). Life-stage and size of the organisms at test start were not documented. Finally, for the morphological alterations, the control values were not reported.

Edition No.: M-813605-01-1

Author	Fernandez Carolina; Asselborn Viviana; Parodi Elisa R
Source	Anais da Academia Brasileira de Ciencias, (2021) Vol. 93, No. 4, pp. e20200233. Electronic Publication Date: 9 Aug 2021 Journal code: 7503280. E-ISSN: 1678-2690. L-ISSN: 0001-3765.
Title	Toxic effects of chlorpyrifos, cypermethrin and glyphosate on the non-target organism Selenastrum capricornutum (Chlorophyta).
Publication Year	2021
Accession Number	2024432423 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This study evaluates the acute toxic effects of glyphosate on the growth, biovolume and ultrastructure of the green microalgae *Selenastrum capricornutum*. After 48 h, all tested concentrations reduced significantly the population growth. The regulatory relevant endpoint 96 h effective concentration 50 (EC50) was 15.60 mg/L. Cells exposed to glyphosate showed an increase in the cellular size related to the increase in pesticide concentration and exposure time. The most significant damages observed on the ultrastructure of cells included thylakoids and mitochondria disruption, formation of electrodense bodies, accumulation of lipids and increase in the size and number of starch granules.

The study is considered reliable with restrictions because it lacks analytical verifications of the tested item in the test medium during the exposure phase and the test item is not fully documented.

Edition No.: M-813540-01-1

Author	Arsene, Mathieu Houssou ; Cocan, Daniel ; Raducu, Camelia Maria ; Eric Joslin Daguegue; Miresan, Vioara ; Montchowui, Elie
Source	Processes, Vol. 9, No. 4, 20210101 E-ISSN: 2227-9717 DOI: 10.3390/pr9040701 Published by: MDPI AG, Basel
Title	Acute and Chronic Effects of a Glyphosate and a Cypermethrin-Based Pesticide on a Non-Target Species Eucypris sp. Vavra, 1891 (Crustacea, Ostracoda)
Publication Year	2021
Accession Number	2021:254291 PQSCITECH
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This article reports the acute and chronic effects of a glyphosate-based pesticide on the fresh-water Ostracoda species *Eucypris* sp. (aquatic invertebrate species other than *Daphnia magna*). The study seems to have been well conducted and reports regulatory relevant and reliable endpoints: 48-h acute LC_{50} = 9.03 mg/L and 28-d chronic LOEC = 0.903 mg/L (10% of the estimated 48-h LC_{50}).

However, the study cannot be considered as fully reliable because it lacks analytical verifications of the tested item in the test medium. In addition, the culture/test medium is not described.

Edition No.: M-813189-01-1

Author	Gabriel, U. U.; Erondu, E. S.
Source	Animal Research International (2010), Volume 7, Number 2, pp. 1184-1193 ISSN: 1597-3115 Published by: Department of Zoology, University of Nigeria, Nsukka URL (Availability): http://www.ajol.info/index.php/ari/article/view/797 66
Title	Toxicity of roundup (a glyphosate product) to fingerlings of Clarias gariepinus.
Publication Year	2010
Accession Number	2013:65220 CABA
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The effects of Roundup containing 360 g/l glyphosate (equivalent to 480 g/L isopropylamine salt) were tested in an acute test with *C. gariepinus* fingerlings. The 96 hour-LC90 was determined to be 19.91 mg product/L. There is no analytical verification of test concentrations reported and thus the reliability of the endpoint is questionable. The appearance of mucus accumulation on the skin and gills and skin pigmentation recorded in fish in the holding / stock vessels is a clear indicator of stress. Therefore, the condition of the fish used in the test is questionable. The study was not conducted in accordance with a recognised test guideline and was not performed under conditions of GLP. Furthermore, the purity of the formulation roundup is not clearly given as the specification in the full text contains some typing errors. The study is considered reliable with restrictions.

Edition No.: M-813556-01-1

Author	Luo Qi-Hua; Gao Jing; Guo Yi; Dai Ping-Li; Hou Chun-Sheng; Wu Yan-Yan; Diao Qing-Yun Luo Qi-Hua; Liu Chang; Ma Yu-Zhen; Zhou Zhi-Yong
Source	Scientific reports, (2021 Jan 22) Vol. 11, No. 1, pp. 2115. Electronic Publication Date: 22 Jan 2021 Journal code: 101563288. E-ISSN: 2045-2322. L-ISSN: 2045-2322. Report No.: PMC-PMC7822899.
Title	Effects of a commercially formulated glyphosate solutions at recommended concentrations on honeybee (Apis mellifera L.) behaviours.
Publication Year	2021
Accession Number	2023540082 MEDLINE (IN-PROCESS)
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

The study reports on possibly relevant endpoints for the acute bee risk assessment, specifically a 48-hour oral LD_{50} value, as well as behavioural assessments on bees after glyphosate exposure. However, the study has to be deemed reliable with restrictions based on the following aspects: The colonies used for this study were obtained from an apiary about which no further information was provided. This pertains especially to possible pre-existent contaminant exposure of the colonies as well as health aspects regarding bee specific illnesses and treatments. As stated in OECD Guideline 213 (Honeybees, Acute Oral Toxicity Test), "… bees treated with chemical substances, such as antibiotics, anti-varroa, etc., should not be used for toxicity test for four weeks from the time of the end of the last treatment". This aspect cannot be adequately assessed as information on the bee colonies health or possible contaminant contact points is missing from the study report. The reported temperature during the test was 30 ± 1°C, which is outside the temperature range of 25 ± 2 °C recommended in OECD 213. The study report states an observation timeframe of 48 hours, however exact time-points of observation are not reported. Test concentrations were not analytically verified. Lastly, the LD_{50} value was reported without confidence intervals. The certainty on the level of protection offered by the median LD_{50} value can hence not be assessed. Based on the above mentioned aspects, the reliability of the study is restricted.

Edition No.: M-813197-01-1

Author	Thompson Helen M Levine Steven L; Doering Janine; Norman Steve; Manson Philip; Sutton Peter; von Merey Georg
Source	Integrated environmental assessment and management, (2014 Jul) Vol. 10, No. 3, pp. 463-70. Electronic Publication Date: 19 May 2014 Journal code: 101234521. E-ISSN: 1551-3793. L-ISSN: 1551-3777. Report No.: NLM-PMC4285224; PMC-PMC4285224.
Title	Evaluating exposure and potential effects on honeybee brood (Apis mellifera) development using glyphosate as an example.
Publication Year	2014
Accession Number	2014526554 MEDLINE
Overall reliability assessment	Reliable without restrictions

Assessment and conclusion
The Oomen et al. (1992) approach was used to quantify at residues in relevant matrices (pollen, nectar, and larvae) following application of glyphosate at 2.88 kg a.e./ha (400 L water/ha) to flowering *Phacelia tenacetifolia* in large glasshouses. Then brood feeding tests following the Oomen approach, were conducted by feeding 1 L treated sucrose solution at 75 / 150 and 301 mg glyphosate a.e./L directly to honeybee colonies. The study is adequately described and all information to evaluate the study are available. At the time the study was conducted, there were no field level test guidelines adopted for use in the EU. The test did follow a recognised approach and is considered fit for purpose. The study is considered as reliable.

Edition No.: M-813587-01-1

Author	Wee June; Cho Kijong Lee Yun-Sik; Kim Yongeun Son Jino
Source	Toxics, (2021 May 31) Vol. 9, No. 6. Electronic Publication Date: 31 May 2021 Journal code: 101639637. E-ISSN: 2305-6304. L-ISSN: 2305-6304. Report No.: PMC-PMC8226473.
Title	Temperature and Aging Affect Glyphosate Toxicity and Fatty Acid Composition in Allonychiurus kimi (Lee) (Collembola).
Publication Year	2021
Accession Number	2024127445 MEDLINE
Overall reliability assessment	Reliable with restrictions

Assessment and conclusion

This study examined the toxicity of glyphosate with the temperature (20ºC and 25ºC) and aging times (0 day and 7 days) in soil using a collembolan species, *Allonychiurus kimi* (Lee). The degradation of glyphosate in soil was investigated. Fatty acid composition of *A. kimi* was also investigated. The half life of glyphosate was 2.38 days at 20ºC and 1.69 days at 25ºC. At 20ºC with 0 day of aging, the EC50 and NOEC were estimated to be 93.5 and 3.7 mg/kg, respectively. As the temperature and aging time increased, the glyphosate degradation also increased, so no significant toxicity was observed on juvenile production. The proportions of the arachidonic acid and stearic acid decreased and increased with the glyphosate treatment, respectively, even at 37.1 mg/kg, at which no significant effects on juvenile production were observed. The study was conducted according to OECD TG 232 Collembolan Reproduction Test in Soil and is considered reliable with restrictions, the validity criteria cannot be fully checked.