Annex to:

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Annex A – Protocol for the risk assessment on the impact of glyphosate residues in feed on animal health

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1. Introduction

This document represents the protocol for the scientific assessment of the EFSA Pesticides unit on the impact on animal health of glyphosate and its residues in feed. This protocol is being developed with the aim of defining as much as possible before developing the strategy that will be applied for collecting data (i.e. which data to use for the assessment and how to identify and select them), the criteria for appraising the relevant evidence, and the approach for integrating all pieces of evidence in order to draw risk assessment conclusions.

This scientific assessment was chosen as a case-study to test the 4-step approach (plan/carry out/verify/report) for data collection, appraisal and integration, illustrated in the EFSA report on “Principles and process for dealing with data and evidence (EFSA, 2015a, deliverable 1 of PROMETHEUS project – PROmoting METHods for Evidence Use in Scientific assessments). The experience gained with this assessment, as well as with other EFSA case-studies, will serve as guidance for further refinement of the process described in the PROMETHEUS report.

Background

On 12 November 2015, EFSA published its Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. Based on the assessment of the representative uses evaluated, EFSA did not raise concerns as regards harmful effects on animal health.

A significant amount of food and feed is imported into the EU from third countries, including food and feed produced from glyphosate-tolerant genetically modified (GMO) crops. Provided that these products (or parts thereof) are not used exclusively as ingredients for animal feed, the maximum residue levels (MRLs) set under Regulation (EC) No 396/2005 apply. This Regulation has a strong focus on consumer protection, and data related to animal health only are not required. It is desirable to address this issue through a risk assessment focused on animal health.

In the Terms of Reference, EFSA is requested under Article 31 of Regulation (EC) No 178/2002 to assess the available information on glyphosate residues in feed, in particular feed imported from outside the EU (i.e. third countries), e.g. glyphosate-tolerant genetically modified crops, and conclude on the possible impact of those residues on animal health.

EFSA is also requested to ask information from companies involved in the renewal of the approval of glyphosate and MRL applications, and from companies authorised to place feed produced from GMO crops on the EU market. This information will be assessed by Germany (RMS, Rapporteur Member State), and a peer review will be organized by EFSA.

Finally, EFSA is requested to deliver its Scientific Report at the same time as the Reasoned Opinion on the review of the existing MRLs for glyphosate according to Article 12 of Regulation (EC) No 396/2005.
2. Problem formulation

2.1. Objectives of the scientific assessment

The Terms of Reference will be addressed by assessing the health risk for farm animals, in relationship with the presence of residues of glyphosate and its metabolites in feed (including GMO feed). This will imply conducting hazard identification and characterisation, exposure assessment and risk characterisation, as detailed below.

2.2. Target populations

The target populations will include the categories of farm animal species as described in the OECD Guidance document on Residues in Livestock (OECD, 2013):

- Bovine (beef and dairy cows)
- Equine (i.e. horses, asses, mules, hinnies);
- Ovine (sheep) and caprine (goat);
- Swine (breeding and finishing);
- Domestic birds and poultry (i.e. chicken (broiler, layer), turkeys, geese, ducks, ostriches, pigeons).

2.3. Glyphosate residues and route of exposure

The exposure of interest is represented by glyphosate residues ingested via feed of plant origin (including GMO feed) as defined in the peer review of the active substance glyphosate (EFSA, 2015b):

- Glyphosate, or N-(phosphonomethyl)glycine
- AMPA, or (aminomethyl)phosphonic acid
- N-acetyl-glyphosate, or N-acetyl-N-(phosphonomethyl)glycine
- N-acetyl-AMPA, or (acetamidomethyl)phosphonic acid

The term “glyphosate residues” will be used in this document to refer to residues containing glyphosate and/or its metabolites.

2.4. Harmful effects

The current risk assessment is specifically focused on the adverse effects associated with the dietary exposure to glyphosate and its residues.

Any possible adverse effects on animal health will be considered for the risk assessment.

Furthermore, information from ADME studies (on absorption, distribution, metabolism and excretion), genotoxicity or mode of action studies (e.g. effects on gut microbiota or mineral chelating effects) that may be identified during the screening of the literature for relevance will be evaluated as additional supporting evidence.
2.5. Identification of the focused risk assessment sub-questions

This section illustrates the objectives of each risk assessment pillar (i.e. hazard identification, hazard characterisation and exposure assessment) and identifies the risk assessment sub-questions that will be answered and combined for performing the assessment.

The objective of the assessment is to establish whether there is an association between glyphosate and its residues (as defined above in 2.3) and any possible adverse effects on animal health. If an association is demonstrated, a qualitative and, if possible, quantitative description of the relationship between the exposure and the identified adverse effect will be performed. This should include an assessment of dose-response and an evaluation of possible uncertainties; for example, those derived from consideration of the toxicokinetic properties of the compounds and of the inter-species variability in the case of animal data.

The final step of the assessment will identify any dietary exposures from the MRLs Reasoned Opinion exceeding levels of no concern for animal health.

Table 1: Risk assessment (RA) sub-questions to be answered (HI: hazard identification; HC: hazard characterisation; EA: exposure assessment)

| RA step | Number | RA sub-question |
|---------|--------|-----------------|
| HI      | 1      | Is there an association between the oral exposure to glyphosate residues in feed (including GMO feed) and adverse effects in farm animal species? |
| HI      | 2      | Is there an association between oral exposure to glyphosate residues and adverse effects in experimental animals? |
| HI      | 3      | Supporting data: are glyphosate residues associated with in vitro effects in biological material from farm animals? |
| HI      | 4      | Supporting data: what are the ADME data for glyphosate residues in the different farm animal species? |
| HC      | 5      | Is there a dose-response relationship between glyphosate residues ingested in feed (including GMO feed) and adverse effects in farm animals? |
| EA      | 6      | What is the estimated exposure of farm animals to glyphosate residues in feed? |

3. Outline of the risk assessment approach, evidence needs and related sources

For hazard identification and characterisation, direct evidence of adverse effects from in vivo studies on farm animals will be taken into account together with indirect evidence from laboratory animals and in vitro studies. The indirect evidence will mainly come from the peer review conclusion for glyphosate (EFSA, 2015b). If evidence of adverse effects in farm animals supports NOAELs (no
observed adverse effect levels) lower than the ones identified during the peer review of glyphosate, these new NOAELs will be used for the hazard characterisation. Otherwise, the risk assessment will rely upon the NOAELs of the peer review (EFSA, 2015b).

For exposure assessment the data and conclusions of the Reasoned Opinion on the review of the existing MRLs for glyphosate according to Article 12 of Regulation (EC) No 396/2005 will be used. In this Reasoned Opinion, livestock feeding studies will also be presented and might be used to address ADME and/or toxicological endpoints in farm animals.

For hazard characterisation, the relevant NOAEL(s) will be used as point of departure to derive a margin of exposure for farm animals.

The evidence needed for each step of the risk assessment, its source and related method for collection, appraisal and synthesis are outlined in Table 2.

**Table 2:** Evidence needs, related sources and method for collecting, appraising and synthesising all pieces of evidence, for each step of the risk assessment process (HI: hazard identification; HC: hazard characterisation; EA: exposure assessment)

| Step       | Evidence Needs                                                                 | Evidence Source                                                                 | Method to Collect, Appraise and Synthesise the Evidence                                                                 |
|------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| **HI and HC** | *In vivo* laboratory animal studies covering toxicological and ADME endpoints | a. EFSA Conclusion October 2015 (EFSA, 2015b) (and any addendum submitted) (Germany, 2015) | For a.: method already defined in the relevant data source                                                                 |
|            | *In vitro* toxicological data                                                   | b. Open literature                                                              | For b.: the literature review conducted by EFSA (see next point) could identify *in vitro* studies on biological material from farm animals |
|            | *In vitro* genotoxicity data                                                   |                                                                                 |                                                                                                                        |
|            | *In vivo* studies with farm animals covering toxicological and ADME endpoints   | a. EFSA Conclusion October 2015 (EFSA, 2015b) (and any addendum submitted) (Germany, 2015) | For a. and b.: method already defined in the relevant data source                                                                 |
|            |                                                                                 | b. Addendum from RMS (Germany, 2017)                                             | For c.: stepwise literature review process done by EFSA, as defined in section 4.1.                                             |
|            |                                                                                 | c. Open literature                                                              |                                                                                                                        |
| **EA**     | Studies assessing levels of glyphosate residues in feed items (including GMO crops). Feed consumption data (OECD, 2013) | Reasoned Opinion on the MRL review (EFSA, 2018)                                 | Method already defined in the relevant data source                                                                       |

### 4. Method for hazard identification and characterisation

For hazard identification and characterisation, direct and indirect evidence from different sources will be integrated. As outlined in the previous section, some evidence as already analysed and synthesized
in the relevant data sources will be used, while for *in vivo* studies on farm animals a literature review will be conducted.

This literature review will follow a structured, stepwise process (as described in section 4.1), and the evidence from the literature will be integrated with the one from EFSA conclusion and MRL opinion, in order to draw hazard identification and characterisation conclusions, and to perform risk assessment for animal health (see section 4.2).

### 4.1. Literature review of studies on livestock

#### 4.1.1. Relevant sub-questions and definition of the eligibility criteria for study selection

For *in vivo* studies on farm animals, the sub-questions that must be answered are formulated as follows:

1. Is there an association between the oral exposure to glyphosate residues in feed (including GMO feed) and adverse effects in farm animal species?
2. Is there a dose-response relationship between glyphosate residues ingested in feed (including GMO feed) and adverse effects in farm animals?

For supporting data, the sub-questions that must be answered are formulated as follows:

3. Are glyphosate residues associated with *in vitro* effects in biological material from farm animals?
4. What are the ADME data for glyphosate residues in the different farm animal species?

The eligibility criteria for selecting the studies relevant to the 4 sub-questions are illustrated in Table 3.

**Table 3:** Eligibility criteria for sub-questions 1 to 4

| Target populations | In | Livestock of all ages and both genders from the following species: |
|--------------------|----|------------------------------------------------------------------|
|                    |    | • Bovine (beef and dairy cows)                                    |
|                    |    | • Equine (i.e. horses, asses, mules, hinnies);                   |
|                    |    | • Ovine (sheep) and caprine (goat);                              |
|                    |    | • Swine (breeding and finishing);                                |
|                    |    | • Domestic birds and poultry (i.e. chicken (broiler, layer), turkeys, geese, ducks, ostriches, pigeons). |
|                    | Out| • All other animal species                                       |
|                    |    | • Humans                                                         |

| Study design / Test system | In | Experimental studies (both on farms and in research centres) with a control group, where glyphosate residues are orally administered to the target population |
|                           | Out| Observational studies (e.g. epidemiological studies) with a control group |
|                           |    | Studies without control group (i.e. Case series/reports) will be identified |
| Exposure/ intervention | In | Out |
|------------------------|----|-----|
| Test material: glyphosate (pure or formulated) or its residues | | as a specific subset |
| Route of exposure: oral | | |
| Levels/Doses: measured or estimated | | |
| Studies, in which animals have been exposed to glyphosate residues, but with unknown level of exposure, will be identified as a specified subset. | | |
| *In vitro* studies with biological material from farm animals will also be identified as a specific subset. | | |
| Out | Studies on isolated co-formulants only |

| Specific outcome of interest | In | Out |
|-----------------------------|----|-----|
| Any adverse effect | | - |
| Any information on a possible mode of action / local effect | | |
| e.g. cell toxicity, genotoxicity, effects on gut microbiota, mineral chelating effects, or other | | |
| Studies where no adverse effects are reported will be identified as a specific subset. | | |
| Studies investigating ADME parameters will also be identified as a specific subset. | | |
| Out | - |

| Language | In | Out |
|----------|----|-----|
| English | | |
| Abstracts should be in English. | | |
| If judged to be relevant: French, Italian, Spanish, Portuguese full-text could be considered by EFSA, a translation should be requested for other languages. | | |

| Time | In | Out |
|------|----|-----|
| Research articles and studies to be included must be published between 1<sup>st</sup> January 1970 and 1<sup>st</sup> January 2017. | | |

| Publication type | In | Out |
|-----------------|----|-----|
| Peer reviewed primary research studies (i.e. studies containing original empirical new data) | | |
| Systematic reviews, reviews and meta-analysis: evaluated as background information and/or used for snowballing (i.e. to retrieve further primary research studies) | | |
| Expert opinions, editorials, letters to the editor | | |
| Articles from the popular media | | |
| Extended abstracts, conference proceedings | | |
| Grey literature | | |
Supplementary evidence could come from the specific subsets identified by applying the eligibility criteria (i.e. studies without control group, studies with unknown level of exposure, *in vitro* studies, studies investigating ADME parameters, and studies where no adverse effects are reported), and will be appraised and synthesised through a narrative approach. In particular, studies reporting no adverse effects will be first appraised to assess whether they are sufficiently powered. If they are not characterised as ‘inconclusive’ they will undergo a full appraisal.

During the scoping and piloting exercise, the screening of studies (title and abstract) performed with GMO plants revealed potential limitations for the assessment of effects on glyphosate on animal health:

- full-text assessment was unlikely to provide an estimated or measured exposure to glyphosate
- most studies referred to performance and focus on the GMO event and not on the glyphosate presence
- no adverse effects were described in these studies

### 4.1.2. Literature searches

The literature searches will be performed with three bibliographic databases: Web of Science Core Collection (selected databases), PubMed and TOXNET.

Preliminary search strategies have been developed for the scoping exercise (see Table A1, Appendix A) to address sub-questions 1 and 2 (hazard identification and characterization). These will be further refined to obtain the final search strings.

The output from the searched databases, i.e. the bibliographic references including relevant information (e.g. title, authors, abstract), will be exported to separate Endnote X8 files, allowing a count of the individual hits per database. Files will then be combined and duplicate records will be removed.

The files obtained will be transferred into a web-based systematic review software, i.e. DistillerSR® (Evidence Partners, Ottawa, Canada).

### 4.1.3. Study selection process

The articles/studies dealing with exposure of farm animals to glyphosate and its residues and retrieved via the literature search (see 4.1.2) will be selected for their relevance in accordance with pre-defined eligibility criteria (see 4.1.1). The whole selection process will be performed in DistillerSR®, applying a two-step procedure:

#### Step 1: Screening of title and abstract

If the information contained in the title or abstract is relevant to the review sub-questions, the article is selected for full-text assessment (step 2). Articles will be excluded during this step if they do not clearly meet at least one eligibility criterion and will be stored in DistillerSR®.

This first step will be conducted in duplicate by the EFSA Group members. In case of doubts or divergences between the two reviewers the article will pass to the second step.
Step 2: Screening of full-text

To confirm whether the references that have passed the first step are relevant to the risk assessment full-texts will be screened against the same eligibility criteria and additional criteria that can be evaluated only on the whole paper.

This second step will be conducted in duplicate by the EFSA Group members and possible disagreements solved by discussion between the reviewers.

The results of the different phases of the study selection process will be reported in a flowchart as recommended in the PRISMA statement on preferred reporting items for systematic reviews and meta-analyses (Moher et al., 2010).

4.1.4. Data extraction from the included studies

For the studies passing the two-step screening described above, specific pieces of information relevant to the structured appraisal process and to the synthesis of the results will be extracted.

Data will be extracted by one reviewer and validated by a second reviewer on the basis of a subset of data extraction. Data extraction forms will be created in DistillerSR® and will be pilot tested with a subset of studies. Draft outlines of the data extraction forms that could be used for collecting the data from the included studies are reported in Table 4.

Table 4: Outline of the data extraction form for *in vivo* studies on farm animals (experimental and observational).

| Study ID | Reference / Title |
|----------|-------------------|
|          | Year the study was conducted (start, if available) |
| Funding  | Funding source(s) |
|          | Reporting of COI by authors |
| Animal model | Species |
|            | Strain / line (where applicable) |
|            | Sex |
|            | Age or physiological state/phase |
| Exposure  | Test compound or mixture administered/exposed to |
|            | Source of chemical (where applicable) |
|            | Purity of chemical |
|            | Dose/exposure levels or concentrations |
|            | Other dose-related details |
|            | Vehicle used for administration (where applicable) |
|            | Route of administration/exposure |
|            | Duration and frequency of dosing/exposure |
| Study design/Methods | Study design |
|                     | Number of groups/ number of animals per group |
|                     | Randomization procedure |
|                     | Allocation concealment |
|                     | Blinding during outcome assessment |
|                     | Use of negative controls and whether controls were untreated, vehicle-treated, or both (where applicable) |
|                     | Endpoint health category (e.g. reproductive) |
| Results            | Main findings per dose or concentration (e.g., mean, median, frequency, measures of precision or variance) |
NOAEL, LOAEL, and statistical significance of other dose levels (author's interpretation) (where applicable)

Shape of dose response if reported by the authors (e.g., description of whether shape appears to be monotonic, non-monotonic, NA for single exposure or treatment group studies)

Applicability / Interpretation of the results (as reported by the authors)

4.1.5. Appraisal of the individual studies

The framework for study evaluation as described on the SciRAP website (www.scirap.org) and the NTP-OHAT Approach for Systematic Review (Rooney et al., 2014) will be considered to develop a tailored tool to appraise the individual studies.

The SciRAP framework proposes a qualitative method including detailed criteria that promote systematic and transparent evaluation of the relevance and reliability of non-standard experimental in vivo studies for the purpose of chemical risk assessment. This is a key step before the weight-of-evidence evaluation can be carried out (Beronius et al., 2014).

According to this approach the reliability of data is closely linked to the reliability of the test method used to generate the data but its assessment is also influenced by the reporting quality. As a consequence, the SciRAP tool recommends first an evaluation of the reporting quality of the study before moving into the evaluation of methodological quality. Evaluation of reporting quality may identify studies that have obvious deficiencies and/or are too poorly reported to allow for thorough evaluation of methodological quality.

In such a framework the evaluation of both reporting and methodological quality is conducted, separately, in two steps:

1) weighting of criteria: certain criteria may be considered more or less critical in specific cases, and the evaluator can determine the relative “weight” each criterion should be given for the study under consideration.

2) evaluation of reporting/methodological quality: a list of criteria is proposed to address several aspects of the study, which are grouped by the following domains: test compound and controls, animal model and housing conditions, dosing and administration of the test compound, data collection and analysis and other. The proposed answers are “Yes”, “Partially”, “No” or “Not determined” and refer to whether the criterion is reported (in the case of reporting quality) or fulfilled (in the case of methodological quality).

In the current assessment a modified approach of the above framework will be applied:

3) weighting: equal weights will be assigned to all criteria by default. Criteria that are not applicable for the specific case or question being assessed may be removed by setting it to “Not applicable” in the tool;

4) evaluation of reporting/methodological quality: the list of criteria will include also items more (or only) relevant to observational study designs and will be simplified to a subset of key elements; it will be carried out using the same rating system as originally proposed;

5) risk of bias: it will be evaluated by tailoring the current OHAT Risk of Bias Tools as included in the NTP-OHAT approach. Its likelihood (definitively or probably high/low risk of bias) will be derived as a combination of the ratings from the assessment of the reporting and methodological quality and translated into the rating scale shown in Table 5; its relation to
methodological quality will be clarified by considering each type of bias in its relevant context (Table 6); whenever a specific bias can be identified as related to an item, its potential impact (i.e. magnitude and direction) on the effect estimates will be evaluated for each case by expert judgment where possible.

The appraisal will include evaluation of quality of reporting, methodological quality, and, consequently, risk of bias and impact on the estimates (where possible). An example of the criteria that could be included is reported in Appendix B. The appraisal will be undertaken by the EFSA working group members, in duplicate. Any discrepancies between them will be discussed in the group. A DistillerSR® form will be developed based on this table to allow a web-based appraisal of the studies.

Table 5: Proposed rating scale for the risk of bias (RoB).

| RoB rating        | Reporting quality rating: reported | Methodological quality rating: fulfilled |
|-------------------|------------------------------------|-----------------------------------------|
| Definitely low    | Yes                                 | Yes                                     |
| Probably low      | Yes                                 | Partially                               |
| Probably high     | Partially                           | Partially                               |
| Definitely high   | Yes                                 | No                                      |

Table 6: Critical appraisal tool for internal validity (risk of bias) (OHAT Risk of Bias Tool, January 2015):

| Question number | Type of bias       | Applicability to experimental animal studies | Questions                                                                 |
|-----------------|--------------------|---------------------------------------------|--------------------------------------------------------------------------|
| 1               | Selection bias     | Y                                           | Was administered dose or exposure level adequately randomized? Randomization requires that each animal had an equal chance of being assigned to any study group including controls |
| 2               | Selection bias     | Y                                           | Was allocation to study groups adequately concealed? Allocation concealment required that research personnel do not know which administered dose or exposure level is assigned at the start of a study. |
| 3               | Selection bias     | N                                           | Did selection of study participants result in appropriate comparison groups? |
| 4               | Confounding bias   | N                                           | Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies? |
| 5               | Performance bias   | Y                                           | Were experimental conditions identical across study groups? |
| 6               | Performance bias   | Y                                           | Were the outcome assessors blinded to study group or exposure level? |
| 7               | Attrition/exclusion bias | Y                                      | Were outcome data completely reported without attrition or exclusion from analysis? |
8. Detection bias | Y | Can we be confident in the exposure characterisation?
9. Detection bias | Y | Can we be confident in the outcome assessment? Are we confident that valid, reliable and sensitive methods to assess the outcome have been consistently applied across groups?
10. Selective reporting bias | Y | Were all measured outcomes reported?
11. Other sources of bias | Y | Other potential threats to internal validity? Were statistical methods appropriate? Did researchers adhere to the study protocol?

4.1.6. Evidence synthesis and uncertainty assessment for studies on farm animals

After the individual appraisal of the studies, evidence will be synthesized taking into consideration the strengths and the weaknesses of the studies constituting the body of evidence.

The results from individual studies on farm animals will be summarised and subjected to an overall integration of the evidence (see Table 7).

Table 7: Evidence synthesis for studies on farm animals

| Study N° | Reporting quality | Methodol. quality | Risk of bias | Test compound | Species | Study | NOAEL / LOAEL (mg/kg bw per d) | Effect identified |
|----------|-------------------|------------------|--------------|---------------|---------|-------|-------------------------------|------------------|
| 1        |                   |                  |              | Glyphosate    |         |       |                               |                  |
| 2        |                   |                  |              |               |         |       |                               |                  |
| 3        |                   |                  |              |               |         |       |                               |                  |

Any supplementary information identified during the literature review will be assessed in a narrative way and considered together with results in Table 9 during evidence synthesis.

4.2. Integration of results from the toxicological assessment from EFSA conclusion and from the RMS’s assessment

Summary tables will be presented for the data in farm animals extracted from the literature review, as well as for the peer reviewed data from the EFSA conclusion (EFSA, 2015b) and MRL opinion. Articles from the literature review already considered during the peer review of glyphosate will not be further considered.

A final data pivot table will be created to plot the NOAEL/LOAEL by endpoint/study (from the literature review) against critical NOAELs/LOAELs from the EFSA conclusion and MRL opinion.

5. Method for exposure assessment

As mentioned previously under chapter 3 (Table 2), the results of the exposure estimates will be taken from the Reasoned Opinion on the MRL review and will be used to identify a margin of exposure for farm animals.
6. Method to assess the uncertainties in the risk assessment

EFSA’s Scientific Committee is developing a guidance document (EFSA, 2016) to offer a toolbox of methodologies – both quantitative and qualitative – for analysing scientific uncertainties in all its scientific assessments. Through the application of this set of methods, EFSA aims to give decision-makers a clearer picture of the scientific uncertainties affecting each assessment.

The draft Guidance identifies the following steps to be followed in order to analyse uncertainties in EFSA scientific assessments:

- Identify sources of uncertainty
- Select which sources of uncertainty to assess individually
- Assess individual sources of uncertainty
- Quantify combined uncertainty (from individual sources)
- Describe un-quantified uncertainties
- Investigate influence/sensitivity
- Decide whether to refine the uncertainty analysis
- Document and report the uncertainty analysis

The draft Guidance identifies two main sources of uncertainty, the ones inherent to the evidence used in the assessment (at the level of each study and across all body of evidence) and the ones related to the assumptions and the structure of the assessment (i.e. the conceptual model).

In the hazard identification and characterization step and in case evidence is retrieved via literature search, the possible sources of uncertainties are identified upfront and listed in the tool used to appraise the risk of bias of each individual study (see Tables 5 and 6 above). They are assessed individually in each study that meets eligibility criteria. Additional uncertainties can affect the overall body of evidence and require evaluation, such as the risk of publication bias and of possible unexplained inconsistencies among study results.

Similarly, uncertainty can arise from the method used to synthesise evidence e.g. when a model is used and assumptions are made in order to apply it.

Finally, uncertainty can arise from the validity of data used to estimate the exposure (i.e. substance occurrence in feed and feed consumption) but also from the methods and model used to estimate the point of departure (e.g. NOAEL, BMD, etc.).

7. Approach for reaching risk characterisation conclusions

The general principles of the risk characterisation for chemicals in food as described by WHO/IPCS (2009) will be applied as well as the different EFSA guidance documents relevant to this step of the risk assessment (see section 1.1. above).

8. Plans for updating the literature searches and dealing with newly available evidence

The literature searches performed as detailed in Appendix A will be performed approximately 6 months before the planned date of publication of the Scientific report. Considering the amount of data that has already been taken into account, new literature published during these 6 months is not expected to affect the conclusions on the risk assessment for animal health.
9. Human resources, software and timelines for performing the risk assessment

Tasks for performing the different steps in the risk assessment are shown in Table 8.

Table 8: Allocation of tasks for performing the assessment

| What                                    | Who          | Software     | Timeline (planned)       |
|-----------------------------------------|--------------|--------------|--------------------------|
| **Hazard identification and characterisation** |              |              |                          |
| Search process                          | EFSA         | EndNote      | January – February 2017  |
| Study selection for relevance           | EFSA         | DistillerSR® | January – February 2017  |
| Data extraction                         | EFSA         | DistillerSR® | March – April 2017       |
| Appraisal of relevant studies           | EFSA         | DistillerSR® | March – April 2017       |
| Commenting phase (of RMS’s assessment)  | MSs          | -            | 7 April – 5 May 2017     |
| Experts’ consultation (by teleconference on RMS’s assessment update including results of the literature review performed by EFSA) | EFSA, RMS, MSs | -            | June 2017                |
| **Dietary exposure assessment**         |              |              |                          |
| Review of MRLs                          | EFSA in the framework of MRL review (Evaluating Member State: BfR, Germany) | - | December 2017 |
| **Plans for updating the literature searches** |              |              |                          |
| Update of the searches                  | EFSA         | EndNote      | June - July 2017         |
| Select studies for relevance            | EFSA         | DistillerSR® | June - July 2017         |
| Narrative review of relevant additional studies | All WG members | -            | June - July 2017         |

**Finalisation of the EFSA Scientific Report** : December 2017
10. Plan for reviewing the protocol

In November 2016, feedback on the draft protocol has been sought through a targeted consultation of Member States (MSs).
In January 2017, minor amendments were made to the draft protocol for its implementation.
In September 2017, the history of all amendments applied during the assessment was finalised.

11. History of the amendments

A verification of the compliance to the Protocol was performed as described in the PROMETHEUS Scientific report for the principles and process for dealing with data and evidence in scientific assessments: "During and at the end of the assessment, it should be verified if the process is/was undertaken in compliance with what was planned in the strategy. The reasons for any possible deviations from the strategy should also be assessed". An overview of the chapters where amendments were provided can be seen in the following Table 9, and additional explanations are given below.

Table 9: Amendments to the Protocol

| No | Chapter | Title                                                                 | Implemented by | Protocol refinement     |
|----|---------|----------------------------------------------------------------------|----------------|-------------------------|
| 1) | 4.1.2.  | Literature searches                                                   | EFSA           | Yes                     |
| 2) | 4.1.3.  | Study selection process                                               | EFSA           | Yes                     |
| 3) | 4.1.4.  | Data extraction from the included studies                             | RMS            | Peer review process     |
| 3) | 4.1.5.  | Appraisal of the individual studies                                   | RMS            | Peer review process     |
| 3) | 4.1.6.  | Evidence synthesis and uncertainty assessment for studies on farm animals | RMS            | Peer review process     |
| 4) | 4.2.    | Integration of results from the toxicological assessment from EFSA conclusion and from the MRL Reasoned opinion | EFSA           | Yes                     |
| 5) | 6.      | Method to assess the uncertainties in the risk assessment             | -              | Yes                     |
| 6) | 7.      | Approach for reaching risk characterisation conclusions               | EFSA           | Yes                     |
| 7) | 9.      | Human resources and timelines                                         | EFSA           | Yes                     |

1) Amendment of the literature searches

The search strategy was developed using keywords for two key elements:

- Glyphosate residues
- Target populations: farm animals including bovine, equine, ovine, swine, and domestic birds and poultry.

The outcomes were not included in the search, since there can be great variability in the language used to describe them, and studies might not report outcomes in the title or abstract.

The literature searches were performed in the following databases:
1. Web of Science platform encompassing the following databases:
   - Web of Science™ Core Collection
     - Science Citation Index Expanded (1975-2017/02/15)
     - Social Sciences Citation Index (1975-2017/02/15)
     - Arts & Humanities Citation Index (1975-2017/02/15)
     - Conference Proceedings Citation Index- Science (1990-2017/02/15)
     - Conference Proceedings Citation Index- Social Science & Humanities (1990-2017/02/15)
     - Book Citation Index— Science (2005-2017/02/15)
     - Book Citation Index— Social Sciences & Humanities (2005-2017/02/15)
     - Emerging Sources Citation Index (2015-2017/02/15)
     - Current Chemical Reactions (1970-2017/02/15)
     - Index Chemicus (1993-2017/02/15)
   - BIOSIS Citation IndexSM (1970-2017/02/15)
   - CABI: CAB Abstracts® (1970-2017/02/15)
   - Chinese Science Citation Database SM (1970-2017/02/15)
   - Current Contents ConnectSM (1970-2017/02/15)
   - Data Citation Index SM (1970-2017/02/15)
   - FSTA ® – the food science resource (1970-2017/02/15)
   - KCI-Korean Journal Database (1980-2017/02/15)
   - Russian Science Citation Index (2005-2017/02/15)
   - MEDLINE® (1970-2017/02/15)
   - SciELO Citation Index (1997-2017/02/15)
   - Zoological Record® (1970-2017/02/15)
2. PubMed (1970-2017/02/15) (PubMed site)
3. Toxline

The searches were limited to studies published from 1970 onwards, and, when possible, a language limit was applied to retrieve articles published in English, French, Italian, Spanish and Portuguese. Limits to study design were not applied.

The search strategies were based on the preliminary search strategies to address sub-questions 1 and 2 (hazard identification and characterization) reported in the protocol. These were further refined to obtain the final search strings. The searches were run for all the databases on 15 February 2017. The full search strings can be found in the Appendix C.

The output from the searched databases was exported to separate Endnote X8 files, allowing a count of the individual hits per database, and duplicated records within the same platforms were removed. Files were then combined and duplicate records were removed.

2) Amendment of the study selection process

Some refinements were considered necessary through the implementation of the study selection process as described in Table 10 below.
Table 10: Refinement of eligibility criteria for sub-questions 1 to 4 (See Table 1)

| Eligibility criterion | Original protocol                                                                 | Refinement                                |
|-----------------------|-----------------------------------------------------------------------------------|-------------------------------------------|
| **Study design / Test system** | Studies without control group (i.e. Case series/reports) will be identified as a specific subset | Step 1 – In Step 2 - Out |
| **Exposure/intervention** | Studies, in which animals have been exposed to glyphosate residues, but with unknown level of exposure, will be identified as a specified subset. | Step 1 – In Step 2 - Out |
| Out | Studies on isolated co-formulants only | Out also studies in vitro if the cells are not belonging to the target population |
| **Specific outcome of interest** | Studies where no adverse effects are reported will be identified as a specific subset. | In : in case there is an effect but it cannot be clearly estimated if it should be considered as adverse or no. |
| **Publication type** | Systematic reviews, reviews and meta-analysis: evaluated as background information and/or used for snowballing (i.e. to retrieve further primary research studies) | Step 1 - Out |

Among the selected studies, those not yet considered during previous peer review (EFSA, 2015b) or in the addendum submitted by RMS (Germany) in April 2017 were provided to the RMS for inclusion in the revised addendum (June 2017).

3) Amendment of the data extraction, appraisal and evidence synthesis

According to the original Protocol for the hazard identification and characterisation, it was planned that EFSA would implement all steps of the literature review. For reasons related to time-constraints EFSA implemented the first steps (up to and including the studies selection process) while the next steps were performed by the RMS (Germany) in accordance with the peer review process. Furthermore scientific contributions by the Member States (via comments and participation to a meeting) were included for the appraisal step (and part of the evidence synthesis step).

It is noted that the appraisal of the individual studies was however further considered by EFSA (Pesticides Unit in collaboration with Assessment Methodology Unit), and a draft tool was developed starting on the basis of the SciRAP recommendations (but was not applied in the final assessment due to time constraints).

In this appraisal tool, different sets of questions are applicable according to the study design (experimental or observations), and a calculation is proposed for the estimation of the risk of bias (see Tables 11 and 12).
Table 11: Proposed rating scale for the risk of bias (RoB)

| RoB rating          | Reporting quality rating: reported | Methodological quality rating: fulfilled |
|---------------------|------------------------------------|------------------------------------------|
| Definitely low      | Yes                                | Yes                                      |
| Probably low        | Yes                                | Partially                               |
|                     | Partially                          | Yes                                      |
| Probably high       | Partially                          | Partially                               |
|                     | Partially                          | No                                       |
| Definitely high     | Yes                                | No                                       |

Table 12: Critical appraisal form

| Nº  | Question                                                                 | Study design/Answer                |
|-----|--------------------------------------------------------------------------|-------------------------------------|
| 1.  | Is the study carried out in an experimental setting?                      | Yes / No                            |
| 2.  | Glyphosate: the analytical method to measure the test compound was validated or considered as fit-for-purpose. | O/E                                |
| 2.1 | Is it adequately reported?                                               | Yes / partially / no                |
| 2.2 | Is it fulfilled?                                                         | Yes / partially / no                |
| 2.3 | Risk of bias (calculated)                                               |                                     |
| 3.  | Glyphosate: the test compound or mixture was unlikely to contain any impurities that may significantly have affected its toxicity. | O/E                                |
| 3.1 | Is it adequately reported?                                               | Yes / partially / no                |
| 3.2 | Is it fulfilled?                                                         | Yes / partially / no                |
| 3.3 | Risk of bias (calculated)                                               |                                     |
| 4.  | Animal: housing conditions (temperature, relative humidity, light-dark cycle) were appropriate for the study type. | E                                  |
| 4.1 | Is it adequately reported?                                               | Yes / partially / no                |
| 4.2 | Is it fulfilled?                                                         | Yes / partially / no                |
| 4.3 | Risk of bias (calculated)                                               |                                     |
| 5.  | Animal: the different exposure groups were comparable (in terms of characteristics apart from exposure) | O                                  |
| 5.1 | Is it adequately reported?                                               | Yes / partially / no                |
| 5.2 | Is it fulfilled?                                                         | Yes / partially / no                |
| 5.3 | Risk of bias (calculated)                                               |                                     |
| 6.  | Dosing: the allocation of the animals to different treatments was randomized. | E                                  |
| 6.1 | Is it adequately reported?                                               | Yes / partially / no                |
| 6.2 | Is it fulfilled?                                                         | Yes / partially / no                |
6.3. Risk of bias (calculated)

7. Dosing: the timing and duration of administration/exposure were appropriate for investigating the included endpoints.

|   | Is it adequately reported? | Is it fulfilled? |
|---|---------------------------|-----------------|
| 7.1 | E/O                       | Yes / partially /no |
| 7.2 | E/O                       | Yes / partially /no |
| 7.3 | E/O                       | Yes / partially /no |

8. Analysis: The statistical methods have been clearly described and do not seem inappropriate, unusual or unfamiliar.

|   | Is it adequately reported? | Is it fulfilled? |
|---|---------------------------|-----------------|
| 8.1 | E/O                       | Yes / partially /no |
| 8.2 | E/O                       | Yes / partially /no |
| 8.3 | E/O                       | Yes / partially /no |

9. Other: potential confounding factors were appropriately addressed in the study (either by design, analysis or discussion)

|   | Is it adequately reported? | Is it fulfilled? |
|---|---------------------------|-----------------|
| 9.1 | E/O                       | Yes / partially /no |
| 9.2 | E/O                       | Yes / partially /no |
| 9.3 | E/O                       | Yes / partially /no |

10. Other: any other aspects of study design, performance or reporting that might influence reliability was addressed

|   | Is it adequately reported? | Is it fulfilled? |
|---|---------------------------|-----------------|
| 10.1 | E/O                       | Yes / partially /no |
| 10.2 | E/O                       | Yes / partially /no |
| 10.3 | E/O                       | Yes / partially /no |

4) Amendment of the integration of results from the toxicological and exposure assessment

Done according to the peer review process with all relevant information included in the Scientific Report and Reasoned Opinion (EFSA, 2018), taking into account the involvement of other actors (RMS and MSs), the contribution from another source (MRL review) and the time constraints of the peer review process.

5) Amendment of the approach for the assessment of uncertainty

Not performed because of the time constraints and draft status of the guidance on uncertainty.

6) Amendment of the approach for risk characterisation conclusions

The risk characterisation conclusions were drawn following the peer review procedures, in order to meet the time constraints of the regulatory process. All relevant information was included in the Scientific Report.

7) Amendment of human resources and timelines

Due to the fact that this mandate was a case-study, the planning of human resources and timelines had to be revised (e.g. increased FTEs, deadlines postponed, update of the literature search not provided) in order to take into account the lack of experience and guidance in applying the PROMETHEUS approach and implementation tools in the context of a peer review procedure with specific regulatory deadlines.
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## Appendix A – Preliminary search strings and keywords for the literature searches

### Table A1: Preliminary keywords for the scoping exercise to address sub-questions 1 and 2 (hazard identification and characterization)

| Database                                                                 | String searches related to exposure:                                                                 | String searches related to target population:                                                                 |
|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Web of Science<sup>TM</sup>, encompassing the following databases:       | (1) (glyphosate OR Roundup OR n phosphonomethyl glycine OR N-(phosphonomethyl)glycine                 | (3) Sus scrofa domestica OR pig* OR swine OR sow OR barrow OR gilt OR suidae OR pork OR boar OR hog             |
|   - Web of Science<sup>TM</sup> Core Collection                         | (2) ((AMPA AND metabolite*) OR (glyphosate AND metabolite*) OR (aminomethylphosphonic acid)          | (4) Bos (primigenius) Taurus OR bovine OR bovinae OR cow* OR bull* OR cattle OR calf OR calves OR heifer* OR springer* OR dairy herd* OR weaner* OR feeder* OR yearling* OR stirk* OR beef* OR veal* OR ox* OR steer* OR bullock* |
|   - BIOSIS Citation Index<sup>SM</sup>                                 |                                                                                                      | (5) Equus spp OR equine OR ass OR Equus africanus asinus OR horse* OR Equus                              |
|   - CABI: CAB Abstracts<sup>®</sup>                                     |                                                                                                      |                                                                                                             |
|   - Chinese Science Citation Database<sup>SM</sup>                       |                                                                                                      |                                                                                                             |
|   - Current Contents Connect<sup>®</sup>                                |                                                                                                      |                                                                                                             |
|   - Data Citation Index<sup>SM</sup>                                    |                                                                                                      |                                                                                                             |
|   - FSTA<sup>®</sup> – the food science resource                        |                                                                                                      |                                                                                                             |
|   - KCI-Korean Journal Database                                         |                                                                                                      |                                                                                                             |
|   - MEDLINE<sup>®</sup>                                                 |                                                                                                      |                                                                                                             |
|   - Russian Science Citation Index                                       |                                                                                                      |                                                                                                             |
|   - SciELO Citation Index                                               |                                                                                                      |                                                                                                             |
|   - Zoological Record<sup>®</sup>                                        |                                                                                                      |                                                                                                             |
Appendix B – Critical appraisal tools

**Table B.1**: Evaluation of quality of reporting, methodological quality, risk of bias and impact on estimates (draft proposal)

| #  | Weight | Criteria                                                                 | Applicability depending on study design | Item’s reporting | Items’ fulfilment       | Related bias (if any) | Risk of bias                      | Impact on effect estimate(s) |
|----|--------|--------------------------------------------------------------------------|----------------------------------------|------------------|-------------------------|-----------------------|------------------------|----------------------------------|
|    |        | **Glyphosate and its residues (as test compound), and controls**        | All/Experimental/Observational         | yes/partially/no | yes/partially/no       | e.g. Selection bias    | Definitely low/Probably low/Probably high/Definitely high/   | Towards the null/Away from the null |
| 1 | 2 | The test compound or mixture was unlikely to contain any impurities that may significantly have affected its toxicity. |
|---|---|---|
| 2 | 2 | An appropriate vehicle was used that is not expected to interfere with the absorption, distribution, metabolism, excretion or toxicity of the test compound. |

**Animal welfare and housing conditions**

| 3 | 2 | Housing conditions (temperature, relative humidity, light-dark cycle) were appropriate for the study type. |
|---|---|---|
| 4 | 2 | The number of animals in each cage/pen were appropriate to avoid interferences with the results. |
| 5 | 2 | The feed/diet was unlikely to contain contaminants that could affect study results, such as organic pollutants, other pesticide residues, and mycotoxins, as well as phytoestrogens. |

**Dosing and administration of the test compound**

| 6 | 2 | The allocation of the animals to different treatments was randomized. |
|---|---|---|
| 7 | 2 | The timing and duration of |
Administration/exposure were appropriate for investigating the included endpoints.

8 2 The frequency of administration/exposure is appropriate for investigating the included endpoints.

**Data collection and analysis**

9 2 The allocation of animals to different tests and measurements was randomized.

10 2 Reliable and sensitive test methods were used for investigating the selected endpoints.

11 2 Measurements were collected at suitable time points in order to generate sensitive, valid and reliable data.

12 2 The statistical methods have been clearly described and do not seem inappropriate, unusual or unfamiliar.

**Other**

13 2 Are there any other aspects of study design, performance or reporting that influence reliability? (comment in free text)
## Appendix C – Search strategies

### Pubmed

**Date of the search:** 15/02/2016

**Filters applied:** published from 1970, language English, French, Italian, Portuguese, Spanish

| Set | Query | Results |
|-----|-------|---------|
| #12 | Search #10 AND #3 Filters: Publication date from 1970/01/01; English; French; Italian; Portuguese; Spanish | 176 |
| #11 | Search #10 AND #3 | 179 |
| #10 | Search #9 OR #8 OR #7 OR #6 OR #5 OR #4 | 1240880 |
| #9  | Search "Poultry"[Mesh] OR poultry[tiab] OR Poultry[tiab] OR "domestic bird"[tiab] OR "domestic birds"[tiab] OR (domesticated[tiab] AND (bird[tiab] OR bird[s][tiab]))) OR fowl[tiab] OR fowls[tiab] OR galliform*[tiab] OR wildfowl*[tiab] OR "gallinaceous bird"[tiab] OR "gallinaceous birds"[tiab] OR landfowl*[tiab] OR chicken*[tiab] OR "Gallus gallus"[tiab] OR "Gallus domesticus"[tiab] OR broiler*[tiab] OR capon[tiab] OR capons[tiab] OR cockerel*[tiab] OR hen[tiab] OR hens[tiab] OR pullet[tiab] OR pullets[tiab] OR rooster[tiab] OR roosters[tiab] OR waterfowl*[tiab] OR Anatidae[tiab] OR duck[tiab] OR ducks[tiab] OR mallard*[tiab] OR "Anas platyrhynchos"[tiab] OR Geese[tiab] OR goose[tiab] OR anser*[tiab] OR Branta[tiab] OR coturnix[tiab] OR quail*[tiab] OR "turkey"[tiab] OR meleagris[tiab] OR pigeon*[tiab] OR dove[tiab] OR doves[tiab] OR columb*[tiab] OR ostrich[tiab] OR ostriches[tiab] OR struthio[tiab] | 245909 |
| #8  | Search "Sheep"[Mesh] OR ovis[tiab] OR ovine*[tiab] OR ewe[tiab] OR ewes[tiab] OR lamb[tiab] OR lambs[tiab] OR sheep*[tiab] OR mouflon*[tiab] OR hogget*[tiab] OR ram[tiab] OR rams[tiab] OR tup[tiab] OR tups[tiab] OR "Goats"[Mesh] OR goat[tiab] OR goats[tiab] OR capra[tiab] OR capras[tiab] OR caprin*[tiab] OR buck[tiab] OR bucks[tiab] OR geep[tiab] OR geeps[tiab] OR dam[tiab] OR dams[tiab] OR wether*[tiab] OR wethers[tiab] | 193797 |
| #7  | Search "Equidae"[Mesh] OR equidae*[tiab] OR equus[tiab] OR horse*[tiab] OR equine*[tiab] OR colt[tiab] OR colts[tiab] OR foal[tiab] OR foals[tiab] OR yearling*[tiab] OR gelding*[tiab] OR mare[tiab] OR mares[tiab] OR pony[tiab] OR ponies[tiab] OR stallion*[tiab] OR filly[tiab] OR fillies[tiab] OR ass[tiab] OR asses[tiab] OR mule[tiab] OR mules[tiab] OR donkey*[tiab] OR hinny[tiab] OR hinnies[tiab] | 120212 |
| #6  | Search "Swine"[Mesh] OR swine[tiab] OR "sus scrofa" OR "sus domestica" OR "sus domesticus" OR pork[tiab] OR porcine[tiab] OR porc[tiab] OR pig[tiab] OR pigs[tiab] OR piglet*[tiab] OR sow*[tiab] OR sows[tiab] OR boar*[tiab] OR boars[tiab] OR hog[tiab] OR hogs[tiab] OR gilt[tiab] OR gilts[tiab] | 335839 |
| #5  | Search "Cattle"[Mesh] OR cow*[tiab] OR bovine*[tiab] OR cow*[tiab] OR cows[tiab] OR bull[tiab] OR bulls[tiab] OR calf[tiab] OR calves[tiab] OR heifer*[tiab] OR bullock*[tiab] OR steer*[tiab] OR steers[tiab] OR ox[tiab] OR oxen[tiab] OR (Bos[tiab] AND Taurus[tiab]) OR dairy herd*[tiab] OR dairy breed*[tiab] OR weaner*[tiab] OR weaners*[tiab] OR yearling*[tiab] OR stirk*[tiab] OR stirks[tiab] OR springer*[tiab] OR beef*[tiab] OR veal*[tiab] OR veals[tiab] OR feeder*[tiab]) | 452144 |
### Web of Science. All databases

Date of the search: 15/02/2016

Filters applied: published from 1970, language English, French, Italian, Portuguese, Spanish

| Set | Query | Results |
|-----|-------|---------|
| #13 | #11   | 1,382   |
|     | Reffned by: LANGUAGES: ( ENGLISH OR FRENCH OR SPANISH OR ITALIAN OR PORTUGUESE ) Timespan=1970-2017 Search language=Auto |         |
| #12 | #11   | 1,418   |
|     | Timespan=1970-2017 Search language=Auto |         |
| #11 | #10 AND #3 | 1,453   |
|     | Timespan=All years Search language=Auto |         |
### Glyphosate residues and animal health

| # 10 | #9 OR #8 OR #7 OR #6 OR #5 OR #4 | Timespan=All years | Search language=Auto | 4,627,283 |
|------|----------------------------------|--------------------|----------------------|-----------|

| # 9 | TOPIC: (poultry OR Poultries OR (domestic* NEAR/5 (bird OR birds)) OR fowl OR fowls OR galliform* OR wildfowl OR wildfowls OR "gallinaceous bird" OR landfowl OR landfowls OR chicken* OR "Gallus gallus" OR "Gallus domesticus" OR broiler* OR capon OR capons OR cockerel* OR hen OR hens OR pullet OR pullets OR rooster OR roosters OR waterfowl OR waterfowls OR anatidae OR duck OR ducks OR mallard* OR "Anas platyrhynchos" OR Geese OR goose OR anser OR branta OR coturnix OR quail* OR turkey* OR meleagris OR pigeon* OR dove OR doves OR columb* OR ostrich OR ostriches OR struthio) | Timespan=All years | Search language=Auto | 1,171,495 |

| # 8 | TOPIC: (ovis OR ovine* OR ewe OR ewes OR lamb OR lambs OR sheep* OR mouflon* OR hogget* OR ram OR rams OR tup OR tups OR goat OR goats OR capra OR capras OR caprin* OR buck OR bucks OR geep OR geeps OR dam OR dam OR wether OR wethers) | Timespan=All years | Search language=Auto | 762,437 |

| # 7 | TOPIC: (equidae* OR equus OR horse OR horses OR equine* OR colt OR colts OR foal OR foals OR yearling* OR gelding* OR mare OR mares OR pony OR ponies OR stallion* OR filly OR fillies OR ass OR asses OR mule OR mules OR donkey* OR hinny OR hinnies) | Timespan=All years | Search language=Auto | 392,341 |

| # 6 | TOPIC: (swine OR "sus scrofa" OR "sus domestica" OR "sus domesticus" OR pork OR porks OR porcine OR suidae OR pig OR pigs OR piglet* OR "sow" OR "sows" OR barrow* OR boar OR boars OR hog OR hogs OR gilt OR gilts) | Timespan=All years | Search language=Auto | 1,037,609 |

| # 5 | TOPIC: (cattle OR bovin* OR cow OR cows OR bull OR bulls OR calf OR calves OR heifer* OR bullock* OR steer OR steers OR ox OR oxen OR "Bos Taurus" OR "dairy herd"* OR "dairy breed"* OR weaner* OR yearling* OR stirk OR stirs OR springer* OR beef* OR veal OR veals OR feeder*) | Timespan=All years | Search language=Auto | 1,687,364 |

| # 4 | TOPIC: ((Livestock* OR ((Farm OR farms OR farmed OR farming OR "food producing") NEAR/5 animal*)) OR ruminant*)) | Timespan=All years | Search language=Auto | 1,014,447 |

| # 3 | #2 OR #1 | Timespan=All years | 28,372 |
### Glyphosate residues and animal health

#### Search language=Auto

| # 2 | TOPIC: (("1 aminomethylphosphonic acid" OR "aminomethylphosphonic acid" OR "aminomethyl phosphonic acid" OR amep OR aminomethylphosphonate OR "1066 51 9" OR 1066519 OR (AMPA AND (metabolit* OR pesticide* OR herbicide* OR "N acetyl")) OR acetamidomethylphosphonic OR "acetamidomethyl phosphonic" OR acetylglyphosate) Timespan=All years Search language=Auto | 1,362 |
| # 1 | TOPIC: ((glyphosate OR 1071-83-6 OR "1071 83 6" OR 1071836 OR gliphosate OR glyfosate OR roundup* OR "round up" OR "n phosphonomethyl glycine" OR "n phosphonomethylglycine" OR ((mon OR monsanto) NEAR/3 2139) OR mon2139 OR monsanto2139 OR yerbimat*)) Timespan=All years Search language=Auto | 27,813 |

### Toxline

Filters applied: published from 1970

| Set | Query | Results |
|-----|-------|---------|
| # 10 | ( ("poultry" [kw] OR poultry [na] OR poultries [na] OR "domestic bird" [na] OR "domestic birds" [na] OR "domesticated bird" [na] OR "domesticated birds" [na] OR fowl [na] OR fowls [na] OR galliform* [na] OR wildfowl* [na] OR gallinaceous bird [na] OR landfowl [na] OR chicken* [na] OR "gallus gallus" [na] OR "gallus domesticus" [na] OR broiler* [na] OR capon [na] OR capons [na] OR cockerel* [na] OR hen [na] OR hens [na] OR pullet [na] OR pullets [na] OR rooster [na] OR roosters [na] OR waterfowl* [na] OR Anatidae [na] OR duck [na] OR ducks [na] OR mallard* [na] OR "anas platyrhynchos" [na] OR geese [na] OR goose [na] OR anser [na] OR branta [na] OR coturnix [na] OR quail* [na] OR turkey* [na] OR meleagris [na] OR pigeon* [na] OR dove [na] OR doves [na] OR columb* [na] OR ostrich [na] OR ostriches [na] OR struthio [na] OR poultry [ab] OR poultries [ab] OR "domestic bird" [ab] OR "domestic birds" [ab] OR "domesticated bird" [ab] OR "domesticated birds" [ab] OR fowl [ab] OR fowls [ab] OR galliform* [ab] OR wildfowl* [ab] OR gallinaceous bird [ab] OR landfowl [ab] OR chicken* [ab] OR "gallus gallus" [ab] OR "gallus domesticus" [ab] OR broiler* [ab] OR capon [ab] OR capons [ab] OR cockerel* [ab] OR hen [ab] OR hens [ab] OR pullet [ab] OR pullets [ab] OR rooster [ab] OR roosters [ab] OR waterfowl* [ab] OR Anatidae [ab] OR duck [ab] OR ducks [ab] OR mallard* [ab] OR "anas platyrhynchos" [ab] OR geese [ab] OR goose [ab] OR anser [ab] OR branta [ab] OR coturnix [ab] OR quail* [ab] OR turkey* [ab] OR meleagris [ab] OR pigeon* [ab] OR dove [ab] OR doves [ab] OR columb* [ab] OR ostrich [ab] OR ostriches [ab] OR struthio [ab] ) ) | 143119 |
| # 11 | ( #1 OR #2 OR #3 OR #4 ) | 3998 |
| # 12 | ( #5 OR #6 OR #7 OR #8 OR #9 OR #10 ) | 324636 |
| # 13 | ( #11 AND #12 ) | 194 |
| # 14 | ( #13 ) AND 1970:2017 [yr] | 193 |
| # 9 | ( "sheep" [kw] OR ovis [na] OR ovine* [na] OR ewe [na] OR ewes [na] OR lamb [na] OR lambs [na] OR sheep* [na] OR mouflon* [na] OR hogget* [na] OR ram [na] OR rams [na] OR tup [na] OR tups [na] OR "goats" [kw] OR goat [na] OR goats [na] OR capra [na] OR capras [na] OR caprin* [na] OR buck [na] OR bucks [na] OR glee [na] OR geeps [na] OR dam [na] OR dams [na] OR wether [na] OR wethers [na] OR ovis [ab] OR ovine* [ab] OR ewe [ab] OR ewes [ab] OR lamb [ab] OR lambs [ab] OR sheep* [ab] OR mouflon* [ab] OR hogget* [ab] OR ram [ab] OR rams [ab] OR tup [ab] OR tups [ab] OR goat [ab] OR goats [ab] OR capra [ab] OR capras [ab] OR caprin* [ab] OR buck [ab] OR bucks [ab] OR glee [ab] OR geeps [ab] OR dam [ab] OR dams [ab] OR wether [ab] OR wethers [ab] ) ) | 40275 |
| # 8 | ( "equidae" [kw] OR horses [kw] OR equidae* [na] OR equus [na] OR horse [na] OR horses [na] OR equine* [na] OR colt [na] OR colts [na] OR foal [na] OR foals [na] OR yearling* [na] OR gelding* [na] OR mare [na] OR mares [na] OR pony [na] OR ponies [na] OR stallion* [na] OR filly [na] OR fillies [na] OR ass [na] OR asses [na] OR mule [na] OR mules [na] OR donkey* [na] OR hinny [na] OR hinnies [na] OR equidae* [ab] OR equus [ab] OR horse [ab] OR horses [ab] OR equine* [ab] OR colt [ab] OR colts [ab] OR foal [ab] OR foals [ab] OR yearling* [ab] OR gelding* [ab] OR mare [ab] OR mares [ab] OR pony [ab] OR ponies [ab] OR stallion* [ab] OR filly [ab] OR fillies [ab] OR ass [ab] OR asses [ab] OR mule [ab] OR mules [ab] OR donkey* [ab] OR hinny [ab] OR hinnies [ab] ) ) | 15408 |
| # 7 | ( "swine" [kw] OR swine [na] OR "sus scrofa" [kw] OR "sus scrofa" [na] OR "sus domestica" [na] OR "sus domestica" [ab] OR "sus domestica" OR pork [na] OR porks [na] OR porcine [na] OR pig [na] OR pigs [na] OR piglet* [na] OR sow [na] OR sows [na] OR barrow* [na] OR boar [na] OR boars [na] OR hog [na] OR hogs [na] OR gilt [na] OR gilts [na] OR swine [ab] OR "sus scrofa" [ab] OR "sus domestica" [ab] OR pork [ab] OR porks [ab] OR porcine [ab] OR pig [ab] OR pigs [ab] OR piglet* [ab] OR sow [ab] OR sows [ab] OR barrow* [ab] OR boar [ab] OR boars [ab] OR hog [ab] OR hogs [ab] OR gilt [ab] OR gilts [ab] ) ) | 65755 |
| # 6 | ( "cattle" [kw] OR cattle [na] OR bovin* [na] OR cow [na] OR cows [na] OR bull [na] OR bulls [na] OR calf [na] OR calves [na] OR heifer* [na] OR bullock* [na] OR steer [na] OR steers [na] OR ox [na] OR oxen [na] OR ( bos [na] AND taurus [na] ) OR dairy herd* [na] OR dairy breed* [na] OR weaner* [na] OR yearling* [na] OR stirk* [na] OR stirks [na] OR springer* [na] OR beef* [na] OR veal [na] OR veals [na] OR feeder* [na] OR cattle [ab] OR bovin* [ab] OR cow [ab] OR cows [ab] OR bull [ab] OR bulls [ab] OR calf [ab] OR calves [ab] OR heifer* [ab] OR bullock* [ab] OR steer [ab] OR steers [ab] OR ox [ab] OR oxen [ab] OR ( bos [ab] AND taurus [ab] ) OR dairy herd* [ab] OR dairy breed* [ab] OR weaner* [ab] OR yearling* [ab] OR stirk* [ab] OR stirks [ab] OR springer* [ab] OR beef* [ab] OR veal [ab] OR veals [ab] OR feeder* [ab] ) ) | 71973 |
| # 5 | ( "livestock" [kw] OR "ruminants" [kw] OR livestock* [na] OR "farm animal" [na] OR "farmed animal" [na] OR "farm animals" [na] OR "farmed animals" OR "animal farming" OR "animals farming" OR "food producing animal" OR "food producing animals" OR "ruminant* [na] OR "ruminant" [ab] OR "farm animal" [ab] OR "farm animals" [ab] OR "farmed animal" [ab] OR "farmed animals" [ab] OR "animal farming" OR "animals farming" [ab] OR "ruminant* [ab] OR "food producing animal" [ab] OR "food producing animals" [ab] ) ) | 9207 |
| # 4 | ( ( ( ampa [ab] AND ( metabolite* [ab] OR pesticide* [ab] OR herbicide* [ab] OR "n-acetyl" [ab] ) ) ) ) ) ) ) ) | 54 |
| # 3 | ( ( ( ampa [na] AND ( metabolite* [na] OR pesticide* [na] OR herbicide* [na] OR "n-acetyl" [na] ) ) ) ) ) ) | 35 |
| # 2 | ( "1-aminomethylphosphonic acid" [kw] OR 1066-51-9 [rn] OR "aminomethylphosphonic acid" [na] OR "aminomethylphosphonic acid" ) ) ) ) ) | 179 |
| Rank | Query                                                                 | Results |
|------|----------------------------------------------------------------------|---------|
| 1    | ( ( glyphosate [kw] OR 1071-83-6 [rn] OR glyphosate [na] OR 1071-83-6 [na] OR 1071836 [na] OR glyphosate [na] OR roundup [na] OR "round up" [na] OR "n phosphonomethyl glycine" [na] OR "n phosphonomethylglycine" [na] OR "mon 2139" [na] OR mon2139 [na] OR monsanto2139 [na] OR "monsanto 2139" [na] OR yerbamit [na] OR glyphosate [ab] OR 1071-83-6 [ab] OR 1071836 [ab] OR glyphosate [ab] OR roundup [ab] OR "round up" [ab] OR "n phosphonomethyl glycine" [ab] OR "n phosphonomethylglycine" [ab] OR "mon 2139" [ab] OR mon2139 [ab] OR monsanto2139 [ab] OR "monsanto 2139" [ab] OR yerbamit [ab] ) ) ) | 3964    |