Glyphosate
Renewal Group

BAYER

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June 5, 2020

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Ref. FO/ChG 20-0127:
Answer to ANSES request for sourcing glyphosate active substance and request for further information concerning the ANSES study plan on characterization of glyphosate carcinogenic potential

Madame la Directrice,

In May of 2020, ANSES published the result of its call for tenders[1] regarding the selection of organizations which will run additional studies designed to better characterize the carcinogenic potential of glyphosate according to the study plan published in July 2019[2] . In addition, on May 19th 2020 the Glyphosate Renewal Group (GRG) received ANSES request for information about a source of active substance that could be purchased by the teams involved in the studies.

With regards to the latter, sourcing glyphosate active substance according to the current European specification, we confirm that the GRG is willing to offer glyphosate technical material from one of its members (**appendix 1**). GRG member companies could donate a sample of the requested technical material in the same way it is routinely done for any request by researchers from academia or other independent requestors.

With respect to the study plan shared by ANSES, GRG would ask that the following scientific and regulatory aspects are considered in any future

[1] https://www.anses.fr/fr/content/etude-du-potentiel-canc%C3%A9rog%C3%A8ne-du-glyphosate-l%E2%80%99anses-annonce-la-s%C3%A9lection-des-%C3%A9quipes-0
[2] https://www.anses.fr/fr/content/l%E2%80%99anses-va-lancer-un-appel-d%E2%80%99offres-pour-la-r%C3%A9alisation-d%E2%80%99%C3%A9tudes-sur-le-potentiel

assessment of the data in relation to the regulatory status or classification of glyphosate:

1. Scientific and regulatory validation: most of the study methodologies proposed are novel approaches regarding genotoxicity characterization for the purpose of carcinogenic hazard prediction. Therefore, while the GRG fully supports the use of best science and latest scientific knowledge in assessing and characterizing chemicals, without further regulatory-based validation and guidance on interpretation and application in proper weight of evidence, data from these studies cannot be used for regulatory purposes.

2. Transparency: As with the development of most new scientific approaches, transparency and scientific peer review are important in ensuring proper interpretation and application of data, especially for the regulatory purpose of assessing human health risks. Therefore, the GRG would request that the protocols are made available and that opportunities for scientific dialogue on the proposed methodologies are provided in this process. For further detail please see the attached **appendix 2** with input from toxicologist experts elaborating where additional insight would be valuable.

We understand from the original study plan, issued in July of 2019, that ANSES is in discussions with the National Toxicology Program in the US (US NTP) as US NTP has implemented a similar approach regarding the potential for glyphosate to cause oxidative stress[3]. We believe that it would be important to continue with the outreach to NTP as these scientific communities might benefit from sharing information on technical approaches.

As part of our own commitment to transparency, we also inform you that this letter will be published on our GRG website www.glyphosate.eu.

[3] https://ntp.niehs.nih.gov/ntp/results/pubs/posters/swartz_emgs20190919.pdf

Finally, we would appreciate receiving feed-back from you on this letter and in the meantime send you our very best regards.

Nous vous prions de croire, Madame la Directrice, à l'assurance de nos sentiments distingués.

[redacted]

[redacted]
Glyphosate EU Regulatory Lead, Bayer AG
Chair of the GRG Regulatory Working Group

Appendix 1:

Sources of technical glyphosate active substance

The following companies can provide samples of the specific technical materials as listed below.

Technical material nature	Company	Comments
Glyphosate isopropylammonium	Bayer, Barclay	Only available as a solution in water
Glyphosate potassium	Bayer	Only available as a solution in water
Glyphosate monoammonium	Syngenta	
Glyphosate dimethylammonium	Albaugh	Only available as a solution in water

Use of technical material in the form of glyphosate acid is deemed as not relevant because the pH neutralization which will be triggered by some of the studies will generate the corresponding salt derivatives.

As these technical materials are not commercially available from any retailer, ANSES requests can be addressed to the GRG correspondent who will channel them accordingly.
GRG member companies could donate a sample of the requested technical material in the same way this is routinely done for any request by researchers from academia and other independent requestors.
GRG member companies will provide the sample fully characterized according to GLP with an accompanying GLP analytical certificate.

Appendix 2:

Considerations on the outline of the proposed experimental approach

Regarding the proposed investigations aimed to clarify the carcinogenic potential of glyphosate via a genotoxic or an epigenetic and/or non-genotoxic mechanism, GRG would like to emphasize the following points.

The *in vivo* comet assay can be subject to confounding effects from cytotoxicity or hedgehog type cells and hence clear interpretation of the result can be challenging. Any modifications to the assay can introduce another layer of complexity in the interpretation of the data. In their proposal, the Emergency Collective Expert Appraisal Group (GECU) noted "*In addition, considering the possible mode of genotoxic action via oxidation, the assay should also be conducted as a modified comet assay in which a DNA glycosylase should be added to detect the presence of oxidized DNA bases (e.g., 8-OH-dG) in order to increase the sensitivity of the test to this type of lesion.*" It must be noted that this is a non-standard adaptation of the assay. Indeed, there was considerable discussion of this in the OECD Comet Assay Guideline Working Group and it was concluded not to be sufficiently robust and with insufficient review to include as a standard adaptation in the OECD TG 489. Additionally, it is noted in the OECD TG that "*further work would be needed to adequately characterize the necessary protocol modifications.*" Hence, there is no internationally agreed or recognised consensus protocol for the conduct of the modified in vivo comet assay. It is also relevant to note that a working group on the in vivo comet assay has been established by the HESI Genetic Toxicology Technical Committee to address the emerging interpretive issues becoming apparent with the now wider use of the assay. Due to various confounding factors an in vivo comet assay may give an unclear outcome, from which it is difficult to conclude the genotoxicity position. Additionally, there are other technical aspects associated with the conduct of the standard assay that need to be rigidly controlled. Therefore, the laboratories performing the assay should make public the numbers of studies routinely performed per year (both with and without the non-guideline addition), the number of studies carried out in the tissues of

interest in rats and mice and the range of both the positive and negative control data to provide a robust Historical Control Data (HCD) database as indicated in the OECD TG 489.

The proposed *in vitro* methodologies listed to assess cell stress are used in mechanistic studies, but no detailed experimental conditions have been yet provided and more importantly the criteria for acceptability and validity of these tests and the criteria for positive/negative response have not been provided.

Regarding CTA approach, ECVAM SCIENTIFIC ADVISORY COMMITTEE (ESAC) in 2010 concluded that: "*prior to possible regulatory use there was a need to refine the acceptance and assessment criteria for the assay and to evaluate the test performance through dedicated test trials*". The limitations of CTA may have been superseded by the combined approach CTA + transformics, but to our knowledge this approach thus far has only been applied with two molecules.

Regarding the selected teams to conduct the studies, it is not clear which studies or portions of the studies would be performed by the selected laboratories.