

From: [REDACTED]@radboudumc.nl>
Sent: mercredi 25 octobre 2023 18:41
To: SANTE CONSULT-E4
Subject: Glyphosate, regulatory actions and the possible relation to Parkinson's disease
Attachments: Le Monde_[REDACTED].pdf; Concerns around regulatory actions for pesticides.docx

Importance: High

Follow Up Flag: Follow up
Flag Status: Flagged

Dear [REDACTED]

I am reaching out to you in the hope that we could have a brief discussion around the possible relationship between glyphosate and Parkinson's disease. Please allow me to briefly introduce myself. I am a Professor of Neurology, and I am the director of one of the largest centers of excellence for Parkinson's in the world. I'm also the world's number one author in the field of Parkinson's disease ([Parkinson Disease: Worldwide - Expertscape.com](https://www.expertscape.com/parkinson-disease-worldwide)). And I have many different leadership roles in the international Parkinson community.

I am reaching out to you because I have concerns around the regulatory actions that have led to the proposed approval to extend the use of glyphosate by another 10 years. My concerns are summarized in the attached opinion paper that we published in *Le Monde* recently (attached) and are reiterated in the attached Word document that summarizes the various concerns in English. The key concern is that current screening procedures offer no adequate insight into the risk of Parkinson's disease and other neurodegenerative disorders. Please note that my concerns are shared by respected Parkinson scientist across the globe, and in fact, the shortcomings of the existing regulatory actions have been acknowledged by the EFSA themselves during a recent workshop.

In the lead up to the crucial vote in November 18, I hope to speak to you to discuss a possible way forward. Given the serious concerns around the data gap in relation to neurodegenerative disorders, an extension by 10 years is to my mind an incorrect decision. An immediate ban on glyphosate is the other extreme outcome, which is neither attractive. I'm hoping to discuss an intermediate way forward with you, which would allow us to proceed with the use of glyphosate for a more limited time, while using that same timeframe to perform properly designed experiments that can give us a clear insight into the risk of Parkinson's disease and other neurodegenerative disorders. Such a compromise good to my mind be agreeable to all stakeholders involved and alleviate growing concerns among citizens in Europe around the possible neurotoxic effects of glyphosate.

I would be happy to make myself available at any time you ask for my presence. I look forward to hearing back from you!

With best wishes, [REDACTED]

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MD, PhD, FRCPE, FEAN
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Patient-related questions

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Concerns around regulatory actions for pesticides

We, concerned Parkinson scientists, make an urgent appeal to governments and policy makers throughout the European Union to consider the arguments listed below in preparation for the vote the 16th of November, and to work towards an amended authorization of glyphosate for a briefer period of time, coupled to rigorous neuro- toxicological evaluations.

Our opinion is based on two main considerations, which we illustrate here using Parkinson's disease (PD) as showcase. Importantly, PD is the world's fastest growing neurological disease; the number of people affected by PD is expected to double in the next 20 years, unless we act now. Similar concerns as outlined below likely also apply to other neurodegenerative diseases, such as Alzheimer's or motor neuron disease (ALS), and intellectual disabilities in exposed children.

1. Current regulatory actions are inadequate to assess the risk of neurodegenerative diseases

It is presently impossible to estimate the safety of glyphosate in relation to PD. This is because the current regulatory actions, as defined by the EFSA, have serious shortcomings.

- a. **Current procedures to test for neurotoxicity are far too crude.** The risk of neurodegeneration is assessed primarily by evaluating the occurrence of clinically discernible neurological symptoms in exposed animals. However, in case of PD, symptoms arise only after loss of some 60-70% of brain cells. If, for example, 40% of those cells have died, the test animal would appear to be perfectly healthy, but the pesticide under study is anything but safe. Therefore, the absence of neurological symptoms in such an animal experiment does not exclude the possibility of relevant damage. Targeted post-mortem cell counts in relevant brain regions are therefore necessary, but this is not part of current regulatory actions. This shortcoming had been recognized for many years by international researchers⁵, but are now also acknowledged by the EFSA itself (work conference, September 2022).
- b. **Glyphosate doses used to date are not representative of everyday exposure.** Specifically, the present experiments test glyphosate concentrations that typically reach humans after dietary exposure. However, glyphosate can travel long distances through the air, creating another route of exposure. It has been shown by the international SPRINT study (*Sustainable Plant Protection Transition*), that residues of glyphosate were found to be present in the faeces of 70% in a sample of 700 EU inhabitants. Also, there are high concentrations of glyphosate and other pesticides found in house dust in the homes of farmers, as well as those of residents living nearby farmland, thus creating exposure via the skin and inhalation. These routes of entry and such high concentrations should be considered explicitly when assessing the neurotoxicity of glyphosate.
- c. **The effects of human exposure to 'cocktails' of pesticides is not addressed.** Currently, only isolated pesticides are being assessed. However, the reality is that farmers, nearby residents and ultimately all citizens are exposed to so-called cocktails which contain multiple pesticides. It is unclear what the summed exposure to these different pesticides means for public health, however, recent work showed that co-exposures to different pesticides results in greater neurotoxicity in the brain region involved in PD than a single pesticide¹⁰. These findings

suggest that little can be said about the safety of any of the pesticides that are currently in use, including glyphosate.

- d. **Pesticides such as glyphosate may also be associated with neurodegeneration by affecting the gut microbiome.** It is important to note that glyphosate is an antibiotic. Animal studies have shown changes in bacteria in the gut following exposure to glyphosate⁸. It is possible that such microbial changes could act as the first event triggering a cascade of neurodegenerative processes, spreading from intestinal neurons to the brain⁹. Evaluation of changes in gut microbiome and subsequent downstream neurodegenerative processes should therefore be part of improved regulatory actions.

- e. **Research on glyphosate (and other pesticides) has been conducted by industry itself.** Most of the research in the review file is funded and conducted by the industry itself. The media have recently drawn attention to the fact that industry omits and even hides relevant findings, such as a relevant study had been omitted that linked glyphosate exposure to neurotoxicity in young rats that had been exposed in utero, from the evaluation dossier.

So, taken together, there is a serious "data gap" when it comes to glyphosate and the risk of PD and other neurodegenerative diseases and this gap was not addressed at all in the reassessment dossier.

2. Glyphosate might be a cause of Parkinson's disease

There is concrete evidence that glyphosate could be a possible cause of Parkinson's disease, indicated by four cases studies and three epidemiological studies. In addition, several animal studies also showed a possible link. This evidence is not conclusive, however, there is sufficient evidence to believe that there is a biologically plausible link between exposure to glyphosate and damage to the specific brain region involved in Parkinson's disease. This evidence, taken together with the identified shortcomings in the regulatory actions as well as the rapid growth of PD, is a cause for serious concern.

Conclusion

We would offer the following advice to governments and policy makers throughout the European Union: (1) Vote against renewing the marketing authorization for glyphosate by another 10 years, but instead consider an admission for a much briefer period of time, ideally a maximum of 3 to 5 years. (2) Urge European authorities to release funding for the rapid development of improved regulatory actions, specifically targeting the risk of PD and other neurodegenerative diseases. (3) Have glyphosate evaluated according to this new framework by independent scientific institutions, and immediately include other pesticides currently used in Europe in the same evaluation process. Depending on the outcome, glyphosate can be extended for much longer if proven to be safe, should be banned if proven to be directly neurotoxic to brain areas involved in PD or other neurodegenerative disorders. (4) In parallel, alternatives to the use of pesticides must be vigorously pursued.

The outlined measures will help to protect the European population from PD and other health risks and slow the Parkinson pandemic.

Jaroslav Kuisz Au XXI^e siècle, on assiste au trucage des campagnes électorales, et non du vote lui-même

Rhinocéros, d'Eugène Ionesco, est une étude sur le conformisme. Dans une ville de province du sud de la France, les gens sont transformés en animaux. Cette pièce classique est parfois classée dans la catégorie du théâtre de l'absurde. A tort. Il s'agit d'une métaphore d'un processus réel qui, dans son aspect politique, a pris la forme d'un populisme national. En 2015, les élections démocratiques polonaises ont été remportées par le parti nationaliste Droit et justice (PiS). Presque immédiatement, une crise de l'État de droit a éclaté, quand le gouvernement a pris le contrôle de la justice et des médias. Elle n'a pas pris fin, mais a atteint le niveau de l'Union européenne, qui a ouvert plusieurs procédures contre Varsovie.

En Pologne, après une première vague d'ostracisme politique, de plus en plus de personnes connues ont commencé à soutenir le nouveau gouvernement. De nouvelles figures sont venues grossir les rangs, au départ assez minces, des cadres du PiS. La métaphore de la pièce d'Ionesco s'avère plus durable que le communisme. Le mécanisme de conformisme politique lors de l'installation de régimes non démocratiques est universel. Des amitiés se brisent pour des raisons politiques et des familles sont divisées aussi – un phénomène sinistre décrit par Anne Applebaum dans *Démocraties en déclin. Réflexions sur la tentation autoritaire* (Grasset, 2021).

Le 15 octobre, de nouvelles élections législatives ont lieu en Pologne. Le PiS, bien que toujours fort (entre 30 % et 35 % dans les sondages), n'est pas assez populaire pour gouverner seul. Dans cette situation, Droit et justice peut bénéficier des ressources énormes de l'État, alors

Le politiste estime que l'enjeu des élections polonaises du 15 octobre est de savoir si le pays a déjà franchi la ligne au-delà de laquelle la défaite du parti nationaliste au pouvoir devient presque impossible, comme en Hongrie ou en Turquie

IL EST DIFFICILE D'ÉCHAPPER AUX SPOTS PUBLICITAIRES DU GOUVERNEMENT POLONAIS, MÊME SUR LES RÉSEAUX SOCIAUX

que le PIB polonais augmente depuis trois décennies. L'inégalité des chances entre le gouvernement et l'opposition dans cette élection est frappante. Il suffit de descendre dans la rue ou de consulter n'importe quel média.

Les ministères polonais ont intensifié leur communication. Ils ne cessent d'informer les électeurs, en utilisant les meilleurs emplacements publicitaires, sur les bienfaits du gouvernement pour la santé et la sécurité des Polonais. Sur le bâtiment de la Banque nationale de Pologne, à Varsovie, d'énormes bandeaux publicitaires font l'autopromotion du gouvernement. La forte inflation – 10 % en août, après un taux de 14,4 % en 2022 – par exemple, est simplement imputée à la Russie, en parlant de « put-

inflation ». Les mots pompeux remplacent la réalité, mais les millions de zlotys dépensés sont réels.

Depuis longtemps, la télévision et le radio d'État envoient un message unilatéral qui se résume à une division binaire : le gouvernement est bon, l'opposition est mauvaise. En période de campagne électorale, il y a encore moins de place pour la nuance. Il est difficile d'échapper aux spots publicitaires du gouvernement, même sur les réseaux sociaux. Des publicités agressives visant l'opposition apparaissent pendant qu'on regarde un film ou qu'on écoute ses chansons sur les plates-formes internationales.

Parler sur l'espoir

En 2023, le gouvernement a copié l'idée hongroise de combiner un référendum avec une élection sur des sujets comme l'immigration ou la souveraineté du pays. Il s'agit moins d'attirer les électeurs que de débloquer un flux pratiquement illimité d'argent public pour des campagnes publicitaires sans nuances.

Les politiciens de l'opposition sont allés à la rencontre des électeurs. Ils préparent des campagnes, des interventions électorales, des événements. Deux grandes manifestations de rue – la marche du 4 juin et la Marche d'un million de cœurs, le 1^{er} octobre – ont attiré l'attention des médias étrangers.

Certains sondages suggèrent que l'opposition est susceptible de prendre le pouvoir après les élections. Cela suscite

l'espoir des citoyens qui en ont assez de la politique de Jaroslaw Kaczynski, président du PiS, de Mateusz Morawiecki, premier ministre, et de Zbigniew Ziobro, ministre de la justice. Des élections législatives ont eu lieu en Hongrie en 2022. L'opposition, unie contre Viktor Orban, s'était mise d'accord sur un candidat unique au poste de premier ministre. Peter Marki-Zay a permis à la coalition de progresser dans plusieurs sondages, suscitant l'espoir d'une victoire. En vain.

La même situation s'est produite à l'approche de l'élection présidentielle en Turquie. Le candidat de l'opposition, Kemal Kilicdaroglu, devançait le président Erdogan dans de nombreux sondages. Après vingt ans au pouvoir, on pouvait déjà voir à quel point le pouvoir de cet homme politique vacillait. En vain.

En Hongrie comme en Turquie, l'opposition s'est trouvée confrontée non pas à un autre parti, mais à l'État tout entier et à ses ressources, contrôlées par le parti au pouvoir. Dans une telle situation, il n'est pas question d'égalité des chances dans les campagnes électorales.

La question la plus importante des élections d'octobre en Pologne est la suivante : a-t-on déjà franchi la ligne au-delà de laquelle la défaite du PiS, qui a détourné les ressources de l'État, est impossible ? Au XXI^e siècle, on assiste au trucage des campagnes électorales, et non du vote lui-même. C'est beaucoup plus intelligent. Les organisations internationales ont coutume de se concentrer sur

la probité des élections le jour où les bulletins sont déposés dans les urnes. Or il est déjà trop tard.

Malheureusement, pour de nombreux observateurs des événements, la conclusion peut être la suivante : « La campagne a peut-être été truquée, mais les élections ont été honnêtes. » Cette comparaison peut sembler exagérée, mais prenons le risque : c'est comme espérer acheter un billet de loterie dont les prix ont été volés depuis longtemps.

Et la Pologne en 2023 ? La tragédie des jours à venir vient du fait que nous ne savons pas si, avec une telle inégalité de ressources, l'opposition peut gagner des élections. Et, en même temps, nous ne savons pas non plus si nous sommes déjà dans la situation politique de la Hongrie et de la Turquie. Le drame et l'espoir proviennent donc d'une seule et même source. C'est pourquoi la plupart d'entre nous, citoyens favorables à la démocratie, participeront aux élections, en priant sur l'espoir. Il ne s'agit pas d'un espoir naïf. Car nous nous souvenons que les ennemis de la démocratie libérale la démantèlent au rythme des progrès technologiques et de l'évolution des sociétés. C'est précisément parce que les rhinocéros apprennent aussi des erreurs de leurs prédécesseurs que la pièce d'Eugène Ionesco reste d'actualité. ■

Jaroslav Kuisz est politiste et historien du droit, rédacteur en chef de l'hebdomadaire « Kultura Liberalna ». Il publiera, en novembre, « The New Politics of Poland » (Manchester University Press, 376 p., 29 €)

Bas Bloem et Tjitske Boonstra Il y a de quoi s'inquiéter sérieusement du lien possible entre glyphosate et Parkinson

Alors que la Commission européenne doit valider le renouvellement pour dix ans de l'autorisation de l'herbicide, les deux médecins néerlandais alertent sur la nécessité de développer un nouveau cadre d'évaluation ciblant les risques pour les pathologies neurodégénératives

Le nombre de personnes atteintes de pathologies neurodégénératives telles que les maladies de Parkinson ou d'Alzheimer a fortement augmenté ces dernières années. Parkinson est actuellement la maladie neurologique qui connaît la croissance la plus rapide dans le monde – on parle d'une véritable pandémie. Le nombre de personnes atteintes devrait encore doubler au cours des vingt prochaines années si nous n'agissons pas maintenant.

Cette croissance est en grande partie due aux polluants présents dans notre environnement, tels que les pesticides. Les agriculteurs ont un risque fortement accru de contracter cette maladie, et il en va de même pour les personnes vivant à proximité de parcelles agricoles. En France, le risque de maladie de Parkinson chez les viticulteurs exposés aux pesticides est multiplié par plus de 2,5, et cette pathologie a été reconnue comme maladie professionnelle pour cette population.

Les 12 et 13 octobre, l'Europe devait se prononcer sur le renouvellement de l'autorisation de mise sur le marché du glyphosate, herbicide controversé associé à la perte de biodiversité et à la mortalité des abeilles. En outre, il est

de plus en plus évident que l'utilisation du glyphosate présente des risques pour la santé publique, tels que le cancer. Beaucoup d'entre nous sont exposés quotidiennement au glyphosate ; l'étude internationale Sprint (Sustainable Plant Protection Transition), menée auprès de 700 personnes de toute l'Europe, a révélé que des résidus de glyphosate étaient présents dans les matières fécales de 70 % des participants.

Preuves suffisantes

Le problème est que la politique d'autorisation actuelle, organisée par l'Autorité européenne de sécurité des aliments, présente de graves lacunes. Les animaux de laboratoire sont exposés à des pesticides et le risque de lésions cérébrales est évalué principalement en fonction de l'apparition de symptômes neurologiques observables, c'est-à-dire ayant une traduction sur le comportement des animaux de laboratoire. De tels protocoles sont inadéquats : le cerveau disposant d'une grande capacité de réserve, les symptômes n'apparaissent qu'en cas de dommages importants, c'est-à-dire lorsque 60 % à 70 % des cellules nerveuses de la zone cérébrale impliquée sont endommagées. Si, par exemple,

40 % de ces cellules sont mortes, l'animal testé semble toujours en parfaite santé, mais le pesticide étudié est tout sauf sûr.

Ainsi, l'absence de symptômes neurologiques lors d'une expérience sur des animaux de laboratoire n'exclut nullement la possibilité que des dommages importants se soient produits. Des comptages cellulaires ciblés dans les régions du cerveau impliquées dans la maladie de Parkinson sont nécessaires, mais cela ne fait actuellement pas partie du cadre d'évaluation.

Cette lacune est reconnue depuis des années par des experts internationaux d'instituts de recherche indépendants, mais aussi désormais par les autorités elles-mêmes. En témoigne la conclusion d'une conférence scientifique internationale, en septembre 2022, qui a associé des chercheurs du monde académique et des experts des agences réglementaires. La conclusion de cette réunion était libellée ainsi : « Dans l'ensemble, un large consensus s'est dégagé sur le fait que les procédures actuellement en vigueur, qui font partie des mesures réglementaires existantes, sont susceptibles (...) d'offrir une évaluation inadéquate du risque de développer la maladie de

Parkinson en cas d'exposition de l'homme. » Une deuxième préoccupation est que les doses de glyphosate utilisées jusqu'à présent dans les expériences animales étaient probablement beaucoup trop faibles et non représentatives. Les expériences ont été menées avec des concentrations de glyphosate équivalentes à celles que reçoivent les humains à travers leur alimentation.

Or le glyphosate est aussi présent dans l'air et les poussières, ce qui entraîne une exposition par la peau et par la respiration. Ces voies d'accès et ces concentrations élevées devraient également être explicitement prises

en compte lors de l'évaluation du risque de lésions cérébrales dues à l'herbicide. Enfin, certains s'inquiètent du fait que ces tests et études réglementaires sont menés par l'industrie elle-même.

Il existe aujourd'hui un faisceau de preuves scientifiques indiquant que le glyphosate est une cause possible de Parkinson. Des études sur les animaux montrent que les zones du cerveau concernées par cette pathologie sont endommagées après une exposition à cette substance. Une étude récente a montré que l'exposition au glyphosate était associée à des signes de lésions cérébrales, mesurées par un marqueur sanguin (« neurofilament à chaîne légère ») des lésions cérébrales des maladies de Parkinson et d'Alzheimer, entre autres.

Ces effets ont été observés dans la population générale, c'est-à-dire chez des personnes qui ne travaillaient pas au contact du glyphosate. Ces preuves permettent-elles de conclure ? Non, mais elles constituent des preuves d'un lien dit « biologiquement plausible » entre l'exposition au glyphosate et le risque de maladie de Parkinson. Si l'on ajoute à cela les lacunes du cadre d'évaluation et la croissance rapide de la maladie, il y a de quoi s'inquiéter sérieusement.

En tant que médecins spécialistes des maladies neurodégénératives, nous avons trois conseils à donner à Marc Fesneau, le ministre français de l'Agriculture. D'abord, votez contre le renouvellement de l'autorisation du glyphosate. Ensuite, demandez à l'Europe de débloquer des fonds pour le développement d'un cadre amélioré d'évaluation des pesticides, ciblant les risques de maladie de Parkinson et d'autres pathologies neurodégénératives.

Enfin, faites évaluer le glyphosate et tous les autres pesticides actuellement autorisés par des institutions scientifiques indépendantes. En parallèle, des alternatives aux pesticides doivent être vigoureusement recherchées. Cela protégera votre population et contribuera à freiner la pandémie de Parkinson. ■

Bas Bloem est professeur de neurologie au centre hospitalier de l'université Radboud, Pays-Bas ; Tjitske Boonstra est chercheuse en neurologie à l'université de technologie de Delft et membre de l'Alliance contre Parkinson aux Pays-Bas

M. LE MINISTRE FRANÇAIS DE L'AGRICULTURE, VOTEZ CONTRE LE RENOUVELLEMENT DE L'AUTORISATION DU GLYPHOSATE

From: SANTE CONSULT-E4
Sent: vendredi 27 octobre 2023 13:41
To: [REDACTED]
Cc: SANTE CONSULT-E4
Subject: RE: Glyphosate, regulatory actions and the possible relation to Parkinson's disease

Dear [REDACTED]

Thank you for your message. We propose to have a call to discuss your email and explain some procedural aspects related to the ongoing renewal of approval of glyphosate. We will also invite EFSA to join the call.

We would propose either:

- 9 November at 15.00-16.00 or 16.00-17.00
- 10 November at 11.30-12.30

If you confirm one of these times if suitable for you we will then send a link for the call.

Best regards,

On behalf of [REDACTED]
[REDACTED]



European Commission

Directorate-General for Health and Food Safety

Unit E4 – Pesticides and Biocides

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From: [REDACTED]@radboudumc.nl>
Sent: Wednesday, October 25, 2023 6:41 PM
To: SANTE CONSULT-E4 <sante-consult-e4@ec.europa.eu>
Subject: Glyphosate, regulatory actions and the possible relation to Parkinson's disease
Importance: High

Dear [REDACTED]

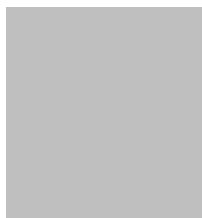
I am reaching out to you in the hope that we could have a brief discussion around the possible relationship between glyphosate and Parkinson's disease. Please allow me to briefly introduce myself. I am a Professor of Neurology, and I am the director of one of the largest centers of excellence for Parkinson's in the world. I'm also the world's number one author in the field of Parkinson's disease (Parkinson Disease: Worldwide - Expertscape.com). And I have many different leadership roles in the international Parkinson community.

I am reaching out to you because I have concerns around the regulatory actions that have led to the proposed approval to extend the use of glyphosate by another 10 years. My concerns are summarized in the attached opinion paper that we published in *Le Monde* recently (attached) and are reiterated in the attached Word document that summarizes the various concerns in English. The key concern is that current screening procedures offer no adequate insight into the risk of Parkinson's disease and other neurodegenerative disorders. Please note that my concerns are shared by respected Parkinson scientist across the globe, and in fact, the shortcomings of the existing regulatory actions have been acknowledged by the EFSA themselves during a recent workshop.

In the lead up to the crucial vote in November 18, I hope to speak to you to discuss a possible way forward. Given the serious concerns around the data gap in relation to neurodegenerative disorders, an extension by 10 years is to my mind an incorrect decision. An immediate ban on glyphosate is the other extreme outcome, which is neither attractive. I'm hoping to discuss an intermediate way forward with you, which would allow us to proceed with the use of glyphosate for a more limited time, while using that same timeframe to perform properly designed experiments that can give us a clear insight into the risk of Parkinson's disease and other neurodegenerative disorders. Such a compromise good to my mind be agreeable to all stakeholders involved and alleviate growing concerns among citizens in Europe around the possible neurotoxic effects of glyphosate.

I would be happy to make myself available at any time you ask for my presence. I look forward to hearing back from you!

With best wishes, [REDACTED]



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Patient-related questions

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From: [redacted]
To: [redacted] (SANTÉ)
Cc: [redacted] Parkinsonalliantie; [redacted]@hotmail.com
Subject: important document for our discussion today
Date: jeudi 9 novembre 2023 13:11:05
Attachments: [redacted] [Lancet Planetary Health \(2023\) Case of glyphosate.pdf](#)
[image001.jpg](#)
[image002.jpg](#)
[image003.png](#)
[image004.png](#)

Dear [redacted],

In this Comment that we just published in Lancet Planetary Health, we express our concerns around the inadequacy of current regulatory actions when it comes to the assessment of the neurotoxicity of pesticides, and particularly in assessing the possible risk of Parkinson's disease and other neurodegenerative disorders, including Alzheimer's disease and amyotrophic lateral sclerosis. We illustrate this for the case of glyphosate and Parkinson's disease. And we conclude with a set of nuanced and balanced recommendations for policy makers, which is now essential in the European Union where a decision will be made on November 16 about the possible renewal of the marketing authorization of glyphosate. But the implications extend well beyond glyphosate, and also beyond Parkinson's disease. Extending the marketing authorization of glyphosate for only a limited time frame, coupled to the urgent development of improved screening procedures, is now an essential step. I look forward to our discussion later today.

with best wishes, [redacted]



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Excellence by the Parkinson's
Foundation

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The inadequacy of current pesticide regulations for protecting brain health: the case of glyphosate and Parkinson’s disease



Parkinson’s disease is undergoing the fastest rise in prevalence among neurological diseases worldwide.¹ This growth is caused in part by exposure to environmental toxicants, with a particular concern revolving around exposure to pesticides. Many pesticides cause nigrostriatal cell death and produce parkinsonian signs in exposed animals. Moreover, farmers have an increased risk of developing Parkinson’s disease.¹

There is an intense debate in Europe around glyphosate, with a vote in November, 2023, on renewing its marketing authorisation. Glyphosate is a controversial herbicide because of concerns around public health risks, including cancer. Many individuals are exposed to glyphosate, with the international SPRINT study finding glyphosate residues in faeces of 70% of participants (farmers, their neighbours, and urban residents).²

We urgently appeal to governments and policy makers throughout the European Union to vote against extending the marketing authorisation of glyphosate by another 10 years. Our opinion is based on two considerations, illustrated here using Parkinson’s disease as an example, although similar concerns apply to other neurodegenerative diseases (eg, Alzheimer’s, motor neuron disease) and intellectual disabilities in children.

Current regulatory actions are inadequate. It is impossible to estimate the safety of glyphosate in relation to Parkinson’s disease because current regulatory actions—defined by the European Food Safety Authority (EFSA)—have serious shortcomings. First, procedures to test for neurotoxicity are too crude. Experimental animals are exposed to pesticides, and neurotoxicity is assessed primarily by evaluating the occurrence of clinically discernible neurological symptoms in exposed animals. However, in case of the nigrostriatal system, parkinsonian signs arise only after extensive damage has been inflicted, after loss of 60–70% of nerve cells. If, for example, 40% of those cells have died, the test animal seems healthy, but the tested pesticide is anything but safe. Therefore, absence of neurological signs in these animal experiments does not exclude relevant damage. Targeted post-mortem cell counts in relevant brain regions are necessary, but are not part of current regulatory actions.

This shortcoming had long been recognised by international researchers, but was also acknowledged in a recent working conference organised by the EFSA:³ “Overall, there was broad consensus that the currently existing procedures, that are part of existing regulatory actions, are likely to give us an inadequate insight into the actual neurotoxic actions of specific pesticides for the substantia nigra, and consequently, offer an inadequate assessment of the risk of developing Parkinson’s disease in case of human exposure.”

Second, glyphosate doses in animal experiments were probably too low and not representative of everyday exposure. The present experiments test glyphosate concentrations that typically reach humans after dietary exposure. However, glyphosate can travel long distances through the air and there are high concentrations of glyphosate and other pesticides in house dust in homes of farmers and residents living nearby farmland,⁴ thus creating exposure via skin and inhalation. These entry routes and such high concentrations should be considered explicitly when assessing glyphosate’s neurotoxicity.

Third, pesticides can cause neurodegeneration by affecting gut microbiome, as shown in animal studies where glyphosate exposure produced changes in intestinal bacteria.⁵ Such microbial changes could act as the first event that triggers a cascade of neurodegenerative processes, spreading from intestinal neurons via the vagal nerve to the brain. Evaluation of changes in gut microbiome and downstream neurodegenerative processes should therefore become part of improved regulatory actions.

Fourth, only isolated pesticides are presently being assessed. However, the reality is that individuals are exposed to so-called cocktails which contain multiple pesticides.² Recent work showed that co-exposures to different pesticides results in greater neurotoxicity to dopaminergic neurons than any single pesticide.⁶ The identified cocktail included pesticides with different mechanisms of action, including compounds that had not raised concerns previously when tested in isolation. These findings indicate that little can be said about the safety of currently used pesticides, including glyphosate.

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Finally, much research on glyphosate has thus far been conducted by industry itself, but they have been shown to omit at least some relevant findings from the evaluation dossier. For example, a relevant study was omitted that linked glyphosate exposure to neurotoxicity in young rats that had been exposed in utero.⁷ Independent studies should therefore be part of the risk evaluation.

Taken together, there is a serious data gap when it comes to glyphosate and the risk of neurological diseases. However, this important knowledge gap was not addressed in the reassessment of glyphosate and the risk of neurological diseases.

Glyphosate might be a cause of Parkinson's disease, as indicated by four case studies (summarised here⁸) and one epidemiological study.⁹ In an animal experiment, co-exposure to glyphosate plus MPTP, a potent neurotoxin that kills dopaminergic neurons, was associated with greater neurotoxicity than exposure to MPTP alone.¹⁰ Furthermore, exposure to glyphosate is associated with higher levels of urinary neurofilament light protein, an indicator of neural damage in neurodegenerative diseases.¹¹ These latter effects were seen in the general population—that is, among people not working with glyphosate professionally. Finally, in vitro studies suggest that glyphosate can cause oxidative stress, neuroinflammation and mitochondrial dysfunction, processes that have all been associated with neurodegeneration in the context of Parkinson's disease.¹²

Overall, the evidence is inconclusive, but sufficient to suggest that there is a biologically plausible link between glyphosate exposure and nigrostriatal cell death, and hence a risk of Parkinson's disease. Together with the identified shortcomings in regulatory actions and the rapid growth of Parkinson's disease, this is cause for serious concern.

We offer the following advice to European Union governments and policy makers: first, vote against renewing the marketing authorisation for glyphosate by 10 years, but consider an admission for a briefer period of time, maximally 5 years. Second, urge European authorities to release funding for rapid development of improved regulatory actions, specifically targeting the risk of Parkinson's disease and other neurodegenerative diseases. Third, have glyphosate evaluated according to this new framework by independent scientific

institutions, and immediately include other pesticides currently used in Europe in the same evaluation. Only pesticides that demonstrate safety according to these new criteria may continue to be used. In parallel, alternatives to the use of pesticides must be pursued vigorously. Such measures will be likely to help protect our population from Parkinson's disease and other health risks.

The RadboudUMC Centre of Expertise for Parkinson & Movement Disorders was supported by a centre of excellence grant from the Parkinson's Foundation. Our funding sources did not have any involvement in the preparation of the manuscript. BRB is co-Editor in Chief for the *Journal of Parkinson's Disease*. He is on the editorial board of *Practical Neurology* and *Digital Biomarkers*, has received honoraria from being on the scientific advisory board for Abbvie, Biogen, and Union Chimique Belge (UCB); has received fees for speaking at conferences from Abbvie, Zambon, Roche, General Electric Healthcare, and Bial; and has received research support from the Netherlands Organization for Scientific Research, the Michael J Fox Foundation, UCB, Not Impossible, the Hersenstichting Nederland, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, and the Parkinson Vereniging (all paid to the institute). TAB is a shareholder in F Hoffmann-La Roche Ltd. The Dutch Parkinson's alliance is supported by AbbVie Netherlands (paid to the institute).

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**Bastiaan R Bloem, Tjitske A Boonstra*
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Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Centre of Expertise for Parkinson & Movement Disorders, PO Box 9101 (947) 6500 HB Nijmegen, The Netherlands (BRB); Dutch Parkinson Alliance, Amersfoort, The Netherlands (TAB)

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(SANTE)

Subject: FW: important document for our discussion today
Importance: High

From: [redacted] <[redacted]@radboudumc.nl>
Sent: Wednesday, November 15, 2023 9:51 AM
To: [redacted] (SANTE) [redacted]@ec.europa.eu>
Cc: [redacted] Parkinsonalliantie [redacted]@parkinsonalliantie.nl>; [redacted]@hotmail.com; [redacted] (EFSA) [redacted]@efsa.europa.eu>; [redacted]@radboudumc.nl>
Subject: RE: important document for our discussion today
Importance: High

Dear [redacted] dear [redacted],

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- A limited extension of the marketing authorisation for glyphosate by just five years is difficult, as this would require a time-consuming process by the European member states.
- Article 21 allows for an intermediate reevaluation, if new insights arise based on new scientific findings.

I was also happy to be able to further explain the concerns that we outlined in a recent publication in Lancet Planetary Health. And I was pleased to hear that we agree that there is currently a data gap when it comes to the possible neurotoxicity of glyphosate in relation to Parkinson's disease and other neurodegenerative disorders, in particular because of a lack of dedicated studies that have looked at the neuronal cell loss in relevant brain areas (the substantia nigra in case of Parkinson's disease). And I was obviously also pleased to hear that there is willingness within the EFSA to collaborate more closely in the near future, in particular around new experiments that will examine the possible neurotoxicity in more detail, taking into account the drawbacks that we identified in our publication in Lancet Planetary Health. Such experiments will obviously require funding, and I also understood that there the EFSA is open to making such funding available.

There is actually an excellent opportunity to begin to shape our collaboration in the near future. I have been invited by Nature Reviews Neurology, a prestigious leading journal in our field, to publish a commentary on the decision that will be reached in Europe around the marketing authorisation of glyphosate in November 16. I think it would be tremendously powerful if we could write this article together with Dr. Tiramani.

I have two concrete questions for you at this point, and I would appreciate a response before tomorrow's vote as I can use this to provide some feedback to the many concerned Parkinson neurologists around the world that I represent.

1. Can you confirm that you will make efforts to secure funding for additional neurotoxicity studies of glyphosate, dedicated specifically to Parkinson's disease and other neurodegenerative disorders?
2. As part of our intention to start working more together, which I really think is an important step forward, would you be interested in being a co-author on a brief commentary for the invited article that will be published later this year in Nature Reviews Neurology?

I look forward to hearing back from you.

with best wishes, [REDACTED]

[REDACTED], MD, PhD, FRCPE, FEAN

Our center is recognised as Center of Excellence by the Parkinson's Foundation

Van: [REDACTED] <[\[REDACTED\]@ec.europa.eu](mailto:[REDACTED]@ec.europa.eu)>

Verzonden: donderdag 9 november 2023 16:50

Aan: [REDACTED] <[\[REDACTED\]@radboudumc.nl](mailto:[REDACTED]@radboudumc.nl)>

CC: [REDACTED] Parkinsonalliantie <[\[REDACTED\]@parkinsonalliantie.nl](mailto:[REDACTED]@parkinsonalliantie.nl)>; [REDACTED] <[\[REDACTED\]@hotmail.com](mailto:[REDACTED]@hotmail.com)>; [REDACTED] <[\[REDACTED\]@efsa.europa.eu](mailto:[REDACTED]@efsa.europa.eu)>

Onderwerp: RE: important document for our discussion today

Dear [REDACTED],

Thank you for your message.

As just mentioned during our call, here's a quick reply with copy to Manuela Tiramani so that you both have each other's email address for the forthcoming cooperation.

Best regards,

[REDACTED]

[REDACTED]



European Commission

Directorate-General for Health and Food Safety
Director E – Food Safety, Sustainability and Innovation

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From: [REDACTED] <[\[REDACTED\]@radboudumc.nl](mailto:[REDACTED]@radboudumc.nl)>

Sent: Thursday, November 9, 2023 1:09 PM

To: [REDACTED] (SANTE) <[\[REDACTED\]@ec.europa.eu](mailto:[REDACTED]@ec.europa.eu)>

Cc: [REDACTED] <[\[REDACTED\]@radboudumc.nl](mailto:[REDACTED]@radboudumc.nl)>; [REDACTED] Parkinsonalliantie

[REDACTED] <[\[REDACTED\]@parkinsonalliantie.nl](mailto:[REDACTED]@parkinsonalliantie.nl)>; [REDACTED] <[\[REDACTED\]@hotmail.com](mailto:[REDACTED]@hotmail.com)>

Subject: important document for our discussion today

Dear [REDACTED]

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with best wishes, [REDACTED]

[REDACTED]



[REDACTED]
[REDACTED]
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Department of Neurology

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From: [REDACTED]@radboudumc.nl>
Sent: Sunday, November 26, 2023 5:55 PM
To: [REDACTED] (SANTE)
Cc: [REDACTED] Parkinsonalliantie; [REDACTED]@hotmail.com; [REDACTED] (EFSA); SANTE CONSULT-E; [REDACTED] (SANTE); [REDACTED] (SANTE); [REDACTED] (SANTE); [REDACTED] (SANTE)
Subject: RE: important document for our discussion today

Thank you kindly for your message [REDACTED]. What you described below is in fact exactly as I had understood your message, I merely abbreviated this considerably in my original message as I wanted to focus on the next steps. I have not heard back from [REDACTED] or anyone else in EFSA yet, but I hope to receive a message soonest, so that we can start our proposed collaboration. As I indicated before, an immediate next step would be a joint publication for *Nature Reviews Neurology*, which we will have to submit in the next weeks. The journal wants to have this paper in print before Christmas. We have already begun writing this important article, in close collaboration with internationally recognized neurotoxicologists, and where we evaluate in detail which studies were considered by the EFSA, and to what extent these have specifically looked at the risk of neurodegeneration. We also evaluate the studies that were initially considered by the EFSA but ultimately not weighed in the final decision. This evaluation will help us in the design of future studies, which brings me to the other important step in our proposed collaboration, which is to reach agreement about additional funding for the development of additional experiments that focus explicitly on the risk of Parkinson's disease and other neurodegenerative disorders. I look forward to hearing back from [REDACTED] in due course.

with best wishes, [REDACTED]

[REDACTED]

Our center is recognised as Center of Excellence by the Parkinson's Foundation

Van: BEREND Klaus <[REDACTED]@ec.europa.eu>
Verzonden: woensdag 22 november 2023 19:42
Aan: [REDACTED]@radboudumc.nl>
CC: [REDACTED] Parkinsonalliantie <[REDACTED]@parkinsonalliantie.nl>; [REDACTED]@hotmail.com; [REDACTED]@efsa.europa.eu; SANTE-CONSULT-E@ec.europa.eu; [REDACTED]@ec.europa.eu>; [REDACTED]@ec.europa.eu>; [REDACTED]@ec.europa.eu>; [REDACTED]@ec.europa.eu>

Onderwerp: RE: important document for our discussion today

Dear [REDACTED]

Thank you for the informative discussion on 9 November and your email below in which you state what you understood from our conversation.

I would like to clarify a bit further what you understood in relation to our explanations why a time period for renewal of 5 years was not considered justified.

The choice of 10 years rather than 5 is not directly related to the time or resources needed to carry out a new review, rather it is related to the added value of doing so.

As explained during our call, applications for renewal of approval must be submitted 3 years before the expiry of an active substance. Therefore, in case of a 5-year renewal period, a full dossier must be submitted 2 years after renewal of approval. As a consequence, there would be little new information available to be included in the comprehensive dossier that applicants must submit and an evaluation of more or less the same information as just completed in July this year would be carried out leading to a significant use of resources with a limited perspective of a significantly different outcome.

On the other hand, a renewal period of 10 years means that a renewal application must be submitted in 7 years, thereby ensuring that a larger amount of new information will be available, leading to a more meaningful new assessment. This would be particularly relevant for your area of work, for which we understood that significant work on developing new methods of examination and testing is planned for the near future – and relevant test results might be available in a couple of years and could then become part of the next renewal process.

I also recall that a review of the approval in accordance with Article 21 of Regulation (EC) No 1107/2009 can be initiated at any time if new evidence emerges – such as from your ongoing work

- that would call into question the approval. Therefore, the 10-year period of renewal is a maximum but can be curtailed if justified.

On the specific points raised to EFSA, I trust that EFSA will respond in due course.

Best regards,

Klaus Berend

Klaus Berend
Director



European Commission

Directorate-General for Health and Food Safety
Director E – Food Safety, Sustainability and Innovation

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Cc: [REDACTED] Parkinsonalliantie <[\[REDACTED\]@parkinsonalliantie.nl](mailto:[REDACTED]@parkinsonalliantie.nl)>;
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[REDACTED] <[\[REDACTED\]@radboudumc.nl](mailto:[REDACTED]@radboudumc.nl)>
Subject: RE: important document for our discussion today
Importance: High

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with best wishes, [REDACTED]

[REDACTED]

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Van: BEREND Klaus <[REDACTED]@ec.europa.eu>

Verzonden: donderdag 9 november 2023 16:50

Aan: [REDACTED]@radboudumc.nl>

CC: [REDACTED] Parkinsonalliantie <[REDACTED]@parkinsonalliantie.nl>;
[REDACTED]@hotmail.com; [REDACTED]@efsa.europa.eu

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Klaus Berend
Director



European Commission

Directorate-General for Health and Food Safety
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e-mail: [\[REDACTED\]@ec.europa.eu](mailto: [REDACTED]@ec.europa.eu)

Web: [Pesticides \(europa.eu\)](https://pesticides.europa.eu); [Biocides \(europa.eu\)](https://biocides.europa.eu)

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From: [\[REDACTED\]@radboudumc.nl](mailto: [REDACTED]@radboudumc.nl)>

Sent: Thursday, November 9, 2023 1:09 PM

To: BEREND Klaus (SANTE) [\[REDACTED\]@ec.europa.eu](mailto: [REDACTED]@ec.europa.eu)>

Cc: [\[REDACTED\]@radboudumc.nl](mailto: [REDACTED]@radboudumc.nl)>; [\[REDACTED\]@parkinsonalliantie.nl](mailto: [REDACTED]@parkinsonalliantie.nl)>; [\[REDACTED\]@hotmail.com](mailto: [REDACTED]@hotmail.com)

Subject: important document for our discussion today

Dear Mr Berend,

In this Comment that we just published in Lancet Planetary Health, we express our concerns around the inadequacy of current regulatory actions when it comes to the assessment of the neurotoxicity of pesticides, and particularly in assessing the possible risk of Parkinson's disease and other neurodegenerative disorders, including Alzheimer's disease and amyotrophic lateral sclerosis. We illustrate this for the case of glyphosate and Parkinson's disease. And we conclude with a set of nuanced and balanced recommendations for policy makers, which is now essential in the European Union where a decision will be made on November 16 about the possible renewal of the marketing authorization of glyphosate. But the implications extend well beyond glyphosate, and also beyond Parkinson's disease. Extending the marketing authorization of glyphosate for only a limited time frame, coupled to the urgent development of improved screening procedures, is now an essential step. I look forward to our discussion later today.

with best wishes, [\[REDACTED\]](mailto: [REDACTED])

[\[REDACTED\]](#)
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Patient-related questions

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Van: [REDACTED]

Verzonden: donderdag 4 januari 2024 12:00

Aan: [REDACTED] <[REDACTED]> @efsa.europa.eu>

CC: [REDACTED] <[REDACTED]> @parkinsonalliantie.nl>;

[REDACTED] <[REDACTED]> @hotmail.com; [REDACTED] <[REDACTED]> @ec.europa.eu>; [REDACTED]

[REDACTED] <[REDACTED]> @ec.europa.eu>;

[REDACTED] <[REDACTED]> @ec.europa.eu>; [REDACTED] <[REDACTED]> @ec.europa.eu>;

[REDACTED] <[REDACTED]> @ec.europa.eu>; [REDACTED] <[REDACTED]> @ec.europa.eu>;

[REDACTED] <[REDACTED]> @ec.europa.eu>; [REDACTED] <[REDACTED]> @radboudumc.nl>

Onderwerp: RE: important document for our discussion today

Dear [REDACTED] dear other colleagues,

Please let me start by wishing a very happy New Year to all of you! I very much look forward working more with you in the coming years.

I thought you would enjoy reading these two new publications. The first is a review paper published in *npj Parkinson's Disease*, where we propose a multitiered approach that allows for a better assessment of the specific risk of neurotoxicity associated with exposure to pesticides, and in particular a possible link with Parkinson's disease.

The second is a commentary published in *Nature Reviews Neurology*, concerning the recent decision to extend the marketing authorization for the use of glyphosate. It offers a very nuanced and balanced perspective on this decision, including an assessment of the uncertainty surrounding possible neurotoxicity associated with the use of glyphosate, and by offering constructive road forward. As we had discussed before, we call for a more intense collaboration between important regulatory bodies such as the EFSA and academic institutions so that we can jointly work to reduce the existing uncertainty.

Both papers have been received very well by the academic community. Please let me know how we can move forward in reaching agreement about the criteria for additional experiments to evaluate the neurotoxicity of glyphosate.

with best wishes, [REDACTED]

[REDACTED]

Our center is recognised as Center of Excellence by the Parkinson's Foundation

Van: [REDACTED] <[REDACTED]@efsa.europa.eu>

Verzonden: donderdag 30 november 2023 09:40

Aan: [REDACTED] <[REDACTED]@radboudumc.nl>

CC: [REDACTED] <[REDACTED]@parkinsonalliantie.nl>;

[REDACTED] <[REDACTED]@hotmail.com>; [REDACTED] <[REDACTED]@ec.europa.eu>; [REDACTED] <[REDACTED]@ec.europa.eu>; [REDACTED] <[REDACTED]@ec.europa.eu>; [REDACTED] <[REDACTED]@ec.europa.eu>; [REDACTED] <[REDACTED]@ec.europa.eu>; [REDACTED] <[REDACTED]@ec.europa.eu>

Onderwerp: RE: important document for our discussion today

Dear [REDACTED]

I would also like to thank you for the meeting held virtually a couple of weeks ago and would like to come back to the two questions addressed to EFSA in your follow-up email.

On the funding question, it is important to note that while EFSA funds projects aimed at improving its methodologies (we have been working for the last 10 years on the neurotoxicity of PPPs and are currently investing approximately 3.5 million Euros on an ongoing project (<https://etendering.ted.europa.eu/cft/cft-display.html?cftId=13967>), it does not fund research.

This is generally in the remit of the European Commission's Directorate for research (DG RTD) https://commission.europa.eu/about-european-commission/departments-and-executive-agencies/research-and-innovation_en#responsibilities.

A specific path to explore funding opportunities could be through the European Partnership for the Assessment of Risks from Chemicals (PARC) <https://www.eu-parc.eu/>. PARC aims to develop next-generation chemical risk assessment to protect human health and the environment, through the promotion of European cooperation, advanced research and increased knowledge of chemical risk assessment.

In light of the above, we can commit to provide support as needed with our expertise, including initiating the dialogue with potential sources of funding in DG RTD and/or PARC.

Coming to your second question: considering the nature of the article (which we understood is, in essence, a review/analysis of EFSA's work on glyphosate) we believe it is more appropriate not to be involved at this stage and, potentially, follow-up once the article is out.

As discussed we believe that a good way to establish formal collaboration would be the mutual presence in the steering committees of each other's projects. We would also be happy to have one of your collaborators with us for a period of time as guest scientist, to see what we do and how we work. We can follow-up bilaterally on this last proposal if interesting to you.

I take the opportunity to also inform you that we have asked the Lancet a right to reply to the commentary you signed and which was published few weeks ago.

Best regards

[REDACTED]

~~~~~

[Redacted]



Parma (IT)

[Redacted]

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