



# Briefing

## A PAN Europe briefing on the assessment of safeners and synergists in view of the European Commission's draft Regulation

**“Plant protection products – data requirements and gradual review of safeners and synergists.”**

**Summary** : According to EU Regulation on Pesticides (Reg. (EC) 1107/2009), pesticides placed on the EU market should have no harmful effects to human and animal health and no unacceptable effects to the environment (Art.1 & 4). This concerns pesticide products and all their ingredients including active substances, safeners, synergists and co-formulants.

Although Article 4 applies to safeners and synergists, an established work programme and data requirements for these substances used in EU pesticide products has been pending since December 2014. Therefore, their risk assessment is still performed at the national level, with unclear methodologies across Member States and level of protection.

In November 2023, after almost 10-years delay the European Commission finally published [a draft Regulation](#) to define data requirements & a work programme for the approval of safeners and synergists. It was open for feedback until December 20, 2023 and could be voted on by European Member States by the end of January in the upcoming meeting of the Standing Committee of Plants Animals Food and Feed (SCoPAFF).

Despite the immense delay, PAN Europe welcomes the proposal for a harmonised EU assessment of safeners and synergists, aligned with that of pesticide active substances. These biologically active substances are equally sprayed onto our food and in the environment, therefore it is important to set the same standard of risk assessment as for active substances in pesticide products.

However, the proposed draft Regulation has limitations that need to be addressed to ensure compliance with the safety provisions of the EU Regulation on Pesticides. These include an extensively lengthy 6.5 years period to review the safeners and synergies currently on the market, the lack of setting protective Maximum Residue Levels for residues of these substances in food or specific limits for groundwater. Above all, it is important to explicitly state that safeners and

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synergists should have no harmful effects on human and animal health, and/or the environment and that their regulation is underpinned by the precautionary principle.

## Introduction

The EU Regulation on Pesticides (Reg. (EC) 1107/2009) aims “to ensure a high level of protection of both human and animal health and the environment” (recital 8) and applies to pesticide products, “in the form in which they are supplied to the user”, consisting of or containing active substances, safeners, synergists, co-formulants and adjuvants (Art.2). More specifically, Article 4 (§2 & 3) provides that pesticide products or their residues should have no harmful effects to human and animal health and no unacceptable effects to the environment. Although Article 4 and the approval criteria of Annex II also apply to safeners and synergists, a Regulation establishing data requirements and a work programme for the gradual review of synergists and safeners already on the market should have been adopted by December 2014. This was never done, therefore the risk assessment of safeners and synergists has remained performed at the national level, with discrepancies across member states regarding the data requirements for their assessment and the criteria under which they are being authorised.

Currently there are 21 safeners and 13 synergists known to be used in pesticide products authorised in EU member states<sup>1</sup>, for which we don't have any information on whether they have been properly assessed for their toxicity. This is a serious data gap, particularly because pesticide formulations that contain synergists and/or safeners are not thoroughly assessed for their potential impact on human health via long-term toxicity studies, therefore the impact of these substances when used in formulations is also largely unknown. This contradicts the EU case law [C616-17](#) (Blaise ruling), in which the Court of Justice of the EU ruled that a pesticide product can be authorised only if it demonstrated that it has no immediate or delayed harmful effect on human health (§114), and therefore should exhibit no long-term carcinogenicity and toxicity (§115). The Blaise ruling also reaffirms that safeners, synergists and co-formulants contained in pesticide formulations must be subject to assessments to determine whether they have any harmful effects (§74).

## The European Commission's draft Regulation on safeners and synergists

In November 2023, following almost a 10-year delay, the European Commission published a [draft Regulation](#) to define data requirements for the approval of safeners and synergists (Art.25(3)) and establish a work programme for the gradual review of the ones already on the market (Art.26). This

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<sup>1</sup> <https://oeil.secure.europarl.europa.eu/oeil/spdoc.do?i=32006&j=0&l=en>

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draft Regulation was open for feedback until **December 2023**. The adoption of a Regulation is urgent as a harmonised assessment of safeners and synergists within the EU is severely lacking.

Despite the significant delay, PAN Europe considers the European Commission's draft Regulation satisfactory in terms of setting data requirements at the same high level as for active substances. This is crucial as safeners and synergists are equally sprayed onto our food and in the environment. According to the draft, the data requirements on safeners and synergists include those mandated for active substances under Regulation (EU) No 283/2013 and for plant protection products under Regulation (EU) No 284/2013, as well as studies from the scientific peer-reviewed open literature published within the last 10 years. Additionally supplementary data requirements are requested for the dossier, which are specific to address the function and need of safeners and synergists in pesticide products.

However, the proposed draft Regulation has **limitations that need to be addressed to ensure compliance with the provisions of the EU Regulation on Pesticides**.

### **Main comments on the draft Regulation**

- 1. Additional lengthy delays in the regulation of safeners and synergists:** the proposed timeline for the work programme for the gradual review of safeners and synergists currently on the market is excessively lengthy: 6.5 years. The Commission has to adopt the work programme in 18 months from the date of entry into force of the text. In the meantime applicants for the approval of a safener or a synergist have to submit the application for approval of the safeners and synergists to the rapporteur Member State 48 months from the date of entry into force. Safeners and synergists are expected to be reviewed within five years of the adoption of the work programme. The timeline foreseen is unacceptably long, and the ground of justification is simply insufficient. The draft Regulation specifies that the length of the procedure for review is "*To ensure alignment with the derogation provided for in Article 81(1) of Regulation (EU) No 1107/2009*". This article provides that "*a Member State may, for a period of 5 years following the adoption of the programme referred to in Article 26, authorise the placing on the market in its territory of plant protection products containing safeners and synergists, which have not been approved, where they are included in that programme.*" However, Article 26 specified that the work programme should have been adopted by 14 December 2014. Therefore the complete review of safeners and synergists should have been completed by 14 December 2019, had article 26 been respected. Provided that the final regulation on safeners and synergists would be adopted next year, this would mean that their review would not be complete before 6.5

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years, which could bring us to 2030. This is particularly concerning given that the safeners and synergists currently authorised in the EU are being evaluated on the basis of different data requirements and authorised on different criteria between Member States, and therefore their toxic properties could be largely unknown.

2. **No food residue safety limits for safeners and synergists:** For the data requirements, the draft act includes the identification and proposal of a residue definition for safeners and synergists, where relevant. However, the draft act does not foresee setting Maximum Residue Levels (MRLs) in food. It is important to note that the MRL Regulation states that the cumulative and synergistic effects of the active substance with other pesticide residues should be taken into account<sup>2</sup>. Article 4(2) of the EU Regulation on Pesticides provides that the residues of the plant protection products should not have any harmful effects on human health or animal health. Although this applies to all the substances that the product consists of, including safeners & synergists (as well as co-formulants), to date, only active substances in food are thoroughly assessed and managed, and not safeners, synergists and co-formulants. A reference to set MRLs for safeners and synergists should be included in the legal text.
3. **Authorisation of products containing unregistered safeners and synergists or whose application is invalid, should be withdrawn:** The draft Regulation foresees establishing a list of all of the safeners and synergists already on the market in EU Member States. On the basis of this list, any interested party wishing to submit an application for the approval of a safener or synergist may submit a request for its inclusion in the work programme for gradual review. Once the list of safeners and synergists for which an approval is sought has been established, the Commission will adopt the work programme. The draft act provides that where no request for inclusion in the work programme for gradual review is received, the Commission will adopt a decision stating that the respective safener or synergist is excluded. However, it appears that the pesticide products that contain them would remain on the market for an additional 5 years after the adoption of the work programme. Moreover, if a safener and synergist is included in the work programme but the application submitted is not considered admissible because it does not comply with the data requirements, then the relevant products will also remain on the market for 5 additional years. This is unacceptable and contradicts the provisions of the EU pesticide law aiming to ensure that products and their ingredients cause no harmful effects to humans, animal health and the environment. The authorisations of the pesticide product containing safeners

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<sup>2</sup> Regulation (EC) 396/2005

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and synergists for which no application has been submitted or their application is considered inadmissible, should be withdrawn from the market at national level when the work programme is adopted.

4. **Limit value of 0.1 µg/L for the protection of groundwater should apply to safeners and synergists:** Finally, we welcome the identification of a residue definition for the purposes of risk assessment and enforcement purposes, but a clear reference to Article 4.2 Reg (EC) 1107/2009 and the protection of groundwater is missing. In this respect, the draft Regulation should establish the same limit value of 0.1 µg/L in groundwater for safeners and synergists and their relevant metabolites, as set for active substances. Similarly to active substances, safeners and synergists, their metabolites and degradation products may spread in different environmental compartments (fields, soils, surface water) and may reach the groundwater. Considering that groundwater needs to provide a safe and long-term sustainable source of water, its protection these residues is important.
5. **Strengthening the reference to the protection of human health and the environment:** Although the draft Regulation refers to Article 4 of Regulation (EC) 1107/2009, it is important to specify that the general provisions of Article 1 are applicable. These provisions aim to ensure a high level of protection for human and animal health as well as the environment, are underpinned by the precautionary principle and extend to both safeners and synergists.

## Background information

### What are safeners and synergists?

According to Reg. (EC) 1107/2009, safeners and synergists are defined separately to “active substances”. Safeners are defined as “substances or preparations which are added to a plant protection product to eliminate or reduce phytotoxic effects of the plant protection product on certain plants” while synergists as “substances or preparations which can give enhanced activity to the active substance(s) in a plant protection product” (Art. 2(2) §3).

### Examples on the function of safeners and synergists

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**Safeners** : Safeners are commonly used in herbicides in order to enhance crop tolerance to the phytotoxicity of the active substance, improving herbicide selectivity<sup>3</sup>. They enhance the crops' capability for metabolic detoxification of herbicides by "exacerbating herbicide-degrading pathways reputedly specifically in crops"<sup>4</sup>. Therefore, safeners are bioactive compounds and are applied as seed treatments or in herbicide-safeners mixtures. Almost all safeners work by inducing the expression of genes, which code for enzymes involved in herbicide detoxification. Thereby, herbicides should be degraded rapidly enough to ensure a damaging concentration is not reached for the crop<sup>5</sup>. Safeners have been developed mainly for cereal crops such as maize, rice and sorghum, for example against pre-emergence thiocarbamate and chloroacetanilide herbicides. Bayer CropScience has developed product portfolios (e.g. Atlantis® WG and Laudis®) containing mefenpyr-diethyl to safen wheat and isoxadifen-ethyl to safen maize, respectively<sup>6</sup>. "The actual molecular target(s) of safeners is/are not known and therefore the reasons for species specificity are unclear"<sup>7</sup>. Being bioactive, the assessment of their potential toxicity to non-target species is urgent.

**Synergists** : Synergists are chemicals that in theory lack pesticidal properties on their own but increase the toxicity of pesticides (other chemicals). Most information available refers to insecticide synergists<sup>8</sup>. A commonly used commercial insecticide synergist is the methylene dioxyphenyl compound, piperonyl butoxide (PBO). PBO can be applied several hours before the pyrethroid or neonicotinoid insecticides, leaving the insect pests in a hypersensitive state before exposure to the insecticide<sup>9</sup>. The synergist inhibits metabolic enzymes (P450s and esterases) which hampers the insects' ability to break down the insecticide molecules. Without piperonyl butoxide, insects would be more likely to degrade the insecticide before mortality occurs, and recover from the poisoning<sup>10</sup>. It is argued that these synergists can aid "in keeping pesticide use to a minimum"<sup>11</sup>, although this remains questionable.

<sup>3</sup> Jablonkai, Istvan. 2013. 'Herbicide Safeners: Effective Tools to Improve Herbicide Selectivity'. *Herbicides - Current Research and Case Studies in Use*. doi:[10.5772/55168](https://doi.org/10.5772/55168).

<sup>4</sup> Duhoux, Arnaud et al. 2017. 'Herbicide Safeners Decrease Sensitivity to Herbicides Inhibiting Acetolactate-Synthase and Likely Activate Non-Target-Site-Based Resistance Pathways in the Major Grass Weed *Lolium sp.* (Rye-Grass)'. doi:[10.3389/fpls.2017.01310](https://doi.org/10.3389/fpls.2017.01310).

<sup>5</sup> Rosinger, Christopher. 2014. 'Herbicide Safeners: an overview'. *Deutsche Arbeitsbesprechung über Fragen der Unkrautbiologie und - bekämpfung*. doi:[10.5073/jka.2014.443.066](https://doi.org/10.5073/jka.2014.443.066).

<sup>6</sup> Ibid 5.

<sup>7</sup> Ibid 5.

<sup>8</sup> National Pesticide Information Center (NPIC). 2020. 'Synergists'. URL: <http://npic.orst.edu/ingred/ptype/synergist.html>.

<sup>9</sup> Alptekin, Selkan et al. . 2015. Insecticide synergists: Good or bad for honey bees? *Outlooks on Pest Management*, 26(2), 75–77. doi:[https://doi.org/10.1564/v26\\_apr\\_07](https://doi.org/10.1564/v26_apr_07).

<sup>10</sup> Ibid 9.

<sup>11</sup> Snoeck, Simon et al. 2017. 'The effect of insecticide synergist treatment on genome-wide gene expression in a polyphagous pest'. *Sci Rep* 7, 13440. doi:[10.1038/s41598-017-13397-x](https://doi.org/10.1038/s41598-017-13397-x).

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However, synergists can also have unintended effects. “A frequently reported unanticipated effect is an altered cuticular penetration of the insecticide after pretreatment with a synergist. In some cases, synergists might also inhibit non-target enzyme systems”<sup>12</sup>. For example, it is questioned whether these synergists have harmful effects on honeybees, by inhibiting their defensive detoxifying enzymes and ability to resist the toxicity from insecticides<sup>13</sup>. Therefore the assessment of their potential toxicity to non-target species is urgent.

### The legal framework for safeners & synergists

Article 25(1) of the EU Regulation on Pesticides provides that safeners and synergists are to be approved when the criteria for the approval of active substances, laid down in Article 4 of that Regulation, are fulfilled. Furthermore, Article 25(2) of that Regulation provides that the general rules applicable to the procedure for the approval of active substances set out in Articles 5 to 21 apply to safeners and synergists as well. In addition, Article 25(3) provides that similar data requirements to those applicable referred to in Article 8(4) for the approval of active substances should be defined for the approval of safeners and synergists. According to Article 26, a Regulation establishing data requirements and a work programme for the gradual review of synergists and safeners already on the market in the European Union should have been adopted by 14 December 2014<sup>14</sup>.

When the EU Regulation on Pesticides came into force, a transitional period of five years after the adoption of the work programme referred to in Article 26 (Art. 81(1)) was foreseen, allowing Member States to deal with safeners and synergists at national level. However, in the absence of such a work programme the national legislations have remained in place. Practically, this means that to date EU Member States have been implementing different criteria and assessment methods prior to granting the authorisation for marketing and use of safeners and synergists.

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<sup>12</sup> Ibid 11.

<sup>13</sup> Ibid 9.

<sup>14</sup> In 2020, the Commission's evaluation report of Reg. (EC) 1107/2009 admits a lack of “setting up [...] an approval procedure for safeners and synergists” (p.3). The justification provided by the EU Commission was the lack of resources to conduct the work. In 2019, the Commission explained in a response to a [parliamentary resolution](#) calling for an implementing Regulation that “21 safeners and 13 synergists are known to be used in plant protection products. In particular for safeners, which in most cases act by enhancing the detoxification mechanisms in target organisms, serious and immediate negative effects do not seem likely. Given the requirements of Article 4(3) and 33(3) of Regulation (EC) No 1107/2009 all of these 34 substances need to be in compliance with the approval criteria in Article 4 of the regulation. Therefore, and in the light of resource constraints, the Commission has given priority to the identification of non-acceptable co-formulants.”

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