



Pesticide  
Action  
Network  
Europe

## How to best address cocktails effects in the Pesticide legislation?

October 2021

### Towards the implementation of a Mixture Assessment Factor (MAF): PAN Europe's Position Paper

#### **Background: The protection of EU citizens from pesticide cocktail effects, a legal and political commitment of the EU**

EU citizens and the environment are continuously exposed to many different combinations of chemicals, including pesticide formulations, both in indoor and outdoor environments (food, water, air, etc.). On their own, synthetic pesticide formulations (or plant protection products) already raise significant concerns. However, a combined exposure to several of them is putting both human and environmental health even more at risk due to *“cocktail effects”*.

Although the risk assessment of pesticides mainly relies on the assessment of individual active substances, cocktail effects should be prevented thanks to clear EU legal requirements to address both cumulative (additive) and synergistic effects (greater than the sum of their individual effects) of pesticides and their residues. Article 4(3)(b) of Regulation (EC) No. 1107/2009 on the placing on the market of Plant Protection Products states that an active substance may only be approved on the European market if it has *“no immediate or delayed harmful effect on human health, including that of vulnerable groups, or animal health (...) taking into account known cumulative and synergistic effects”*. Article 14 of Regulation (EC) No. 396/2005 concerning the setting, modifying and deletion of maximum residue levels (MRLs) of pesticides in or on food and feed shall also consider such effects when the assessment methodologies are available.

This commitment has been strongly reiterated in the context of the [EU Chemicals Strategy for Sustainability](#) of which pesticides are part: *“People and other living organisms are daily exposed to a wide mix of chemicals originating from various sources (...) the effect of (these) chemical mixtures needs to be taken into account and integrated more generally into chemical risk assessments”*. However, this strategy also claims that *“the targeted methodology under development in the specific policy area of pesticides is considered a more refined and accurate way to estimate cumulative risk”*.

**PAN Europe disagrees with this second statement. This targeted methodology does not ensure adequate protection of citizens, including vulnerable groups such as children, and the environment. In the light of increasing evidence underlining the importance of considering co-exposures against multiple pesticides/chemicals, PAN Europe instead calls for the implementation of a Mixture Assessment Factor (MAF) of at least 10 in policy and regulatory areas of pesticides.**

- **State of play: The development of an assessment methodology to be implemented from 2030 despite the urgent need for action!**

Despite clear legal requirements since 2005 and a strong political commitment, the cocktail effects of pesticides and their residues have still not been addressed. Since 2008, the European Food Safety Authority (EFSA) has started to develop a “*targeted*” methodology to assess the cumulative effects of pesticide residues in food (MRL Regulation). Since then, only a small part of this work has been finalised (effects on the thyroid and the nervous systems) and it has not been implemented in regulatory practice. In other words, **cumulative effects are still not assessed by EFSA when evaluating active substances and MRLs requests, which leaves the public unprotected.** Furthermore, independent scientific evidence of cumulative effects did not lead, up to now, to any restriction or ban on pesticides in the EU.

As a result, the European Commission and EFSA committed to speed up their work in the [regulatory fitness and performance programme \(REFIT\)](#) for the pesticide legislation. However, according to the [action plan](#) drawn up by EFSA, **conclusive results can only be expected by 2030**, which is too far away. Although we acknowledge the challenges rising from cumulative risk assessment (CRA), it is not tolerable that EU citizens and the environment continue to be exposed to the cocktail effects of pesticides for another 10 years! This is all the truer as we completely disagree with the methodological approach developed by EFSA, which is neither “*refined*”, nor “*accurate*” as stated by the European Commission in its EU Chemical Strategy for Sustainability.

## **1. The inherent biases and shortcomings of the methodology developed by EFSA**

In EFSA’s CRA methodology, substances are grouped according to their toxicological profile (mode of action) in **cumulative assessment groups (CAGs) on the assumption of dose addition for pesticides**<sup>1</sup>. In total, EFSA estimates that CAGs will need to be established for 15 organ systems (for different organ systems), by 2030<sup>2</sup>. This approach is a step forward compared to not taking cocktail effects into account, but it still assumes that the 15 organs function independently in the human body, which is untrue. The three human communication systems (nervous, endocrine and immune), covering every single cell, are the best illustration that the body is a whole, and that, therefore, a ‘silo’ approach is intrinsically limited.

Then, the exposure to each CAG is calculated according to a tiered approach based on a **probabilistic modelling (MCRA), whose results can be easily manipulated.** It consists of probabilistic distribution of average diets against detected residues (based on existing national monitoring data). This system allows data to be averaged, as well as arbitrary cut-off levels (dismissing the highest outcomes) and arbitrary inputs to the model such as assuming that samples below detection levels are equal to zero. The model does not take into account the fact that some people eat higher quantities of specific food than the average or does not take into account that vulnerable people such as the unborn, young children or the elderly have lower detoxification capacities than healthy adult people.

It is worth highlighting that the MCRA is relying on an IT tool that was developed by the EU-funded research program [ACROPOLIS](#), together with the Food Retail umbrella organisation Freshfel. Already in 2011 ([A toxic mixture](#)) and later in 2014 ([A poisonous injection](#)), PAN Europe criticised the **involvement of industry-linked scientists** in this research programme as well as in EFSA’s expert

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<sup>1</sup> [Technical Annex \(europa.eu\)](#)

<sup>2</sup> As mentioned above, only 2 CAGs have been established so far (for the thyroid and the nervous systems).

panels and working groups on CRA. This has clearly influenced the design of this accommodative methodology for the industry, which is neither a science-based nor a realistic tool reflecting an accurate exposure of consumers.

This is also true for the scope of the modelling. It only takes into account the risks arising from **dietary exposure**, while EU citizens are also exposed to diverse pesticides through air, dust, water, etc. Consequently, residues in food are allowed to cover the entire “*pollution space*” in a body. If non-dietary exposures such as residents’ exposure to agricultural fields were considered, the ‘safe’ level defined by EFSA would easily be surpassed.

It is true that the Food Authority intends to start working on non-dietary exposures, but this work is just beginning, is not mentioned as a priority and will focus only on human health rising from cumulative pesticides exposure.

Finally, the MCRA does not take into account cumulative effects related to **exposure to other chemicals, originating from various sources** such as cosmetic products. However, according to the Chemical Strategy for Sustainability, “*the effect of chemical mixtures needs to be taken into account and integrated more generally into chemical risk assessments*”. The scientific literature<sup>3</sup> shows that the exposure thresholds that are considered safe (No-Observed-Adverse-Effect Level) for a substance A can no longer be considered as such when the exposure to this substance A is combined with that of substances B, C, etc. Similarly, the thresholds set for substances B and C do not take into account cocktail effects related to this combined exposure to different substances. This silo approach, therefore, leads to the assessment of active substances and pesticides as safer than they really are in practice.

Therefore, this limited methodology fails in many ways to realistically assess the adverse effects arising from cumulative exposure to different substances and plant protection products. For all these reasons and considering that the EU cannot wait any longer to address chemicals cocktail effects, the implementation of a MAF (mixture assessment factor) constitutes the best and safest tool to immediately and accurately prevent the exposure of citizens to pesticides and other chemicals.

## **2. Recommendation: Towards the immediate application of mixture assessment factor (MAF) in the pesticide policy area in line with the precautionary principle**

A MAF can be defined as the “*factor by which the regulatory threshold of a given chemical (such as NOAELs) needs to be divided in order to ensure a level of protection against unintended mixture effects that is similar to the level of protection aimed for in a single substance assessment*”<sup>4</sup>. It constitutes an **interpretation of the precautionary principle to address the risk of cocktail effects**.

The size of the MAF is determined by the number of mixture components, their individual potency, and their proportion in the mixture. As active substances are by nature mixed with other substances (synergists, safeners) in plant protection products, PAN Europe recommends the implementation of **at least a 10 MAF**. The NOAELs (and thus Acceptable Daily Intake), which are currently overestimated due to a substance-specific approach, would be divided by 10. **This could immediately be**

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<sup>3</sup> J. M. Conley and al., A mixture of 15 phthalates and pesticides below individual chemical no observed adverse effect levels (NOAELs) produces reproductive tract malformations in the male rat, Environment International, Volume 156, 2021, 106615, [ISSN 0160-4120](#).

<sup>4</sup> KEMI (Swedish Chemicals Agency), Improving the regulatory assessment of combination effects: steps towards implementing the mixture assessment factor (MAF) in chemical regulation, Stockholm 2021, [PM 8/21](#).

**implemented by EFSA during its risk assessments, with no further delay with respect to what the Pesticide regulation requires unlike EFSA's current methodology building on CAGs.**

In addition, from being the most protective (providing a determination of a science-based and realistic MAF), this default approach would be the **most pragmatic**. Indeed, alternative methodologies such as EFSA's require infinite data-demanding scenario-specific mixture risk assessments due to the significant number of plant protection products on the EU market and potential combinations thereof.

Moreover, this approach would set a path towards a harmonized assessment of chemicals<sup>5</sup> as it would align the work conducted under the pesticide policy areas on the rest of the EU future revised chemical framework. The Chemical Strategy for Sustainability introduces the MAF as the key tool to assess chemical mixtures, starting with the horizontal framework REACH as well as other sector-specific considered "relevant", but without mentioning the pesticides framework. PAN Europe claims that the pesticide legislation is highly relevant and should not benefit from any exemption to this MAF, especially not when it is to do less while claiming to do more and better.

We note that **the establishment of a MAF is also the option recommended by a significant part of the scientific community<sup>6</sup> and some national regulatory agencies<sup>7</sup>**. It is on this work, informed by scientific knowledge and practical experience, that PAN Europe's own position is based.

## Conclusion

Although PAN Europe is aware of the challenges arising from the cumulative risk assessment, the probabilistic and sectoral approaches developed by EFSA do not ensure adequate protection of consumers, including vulnerable groups such as children, and the environment. Even independently designed, it would never succeed in accurately measuring the risks of pesticide mixtures as **the combinations of risks to be studied scientifically are infinite**.

Rather than persisting with this approach, which will not yield results until 2030 (based on EFSA's action plan), PAN Europe calls for the pragmatic and preventive implementation of a Mixture Assessment Factor (MAF) of 10 when assessing all individual active substances and MRLs applications. Promoted by the Chemical Strategy for Sustainability, such a factor will address all the shortfalls of EFSA's current methodology and strengthen the coordination and communication across regulatory bodies and sectors. **The implementation of this MAF should go hand in hand with a strong and proactive policy to rapidly reduce pesticide use, in line with the [Farm to Fork Strategy](#).**

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**Pesticide Action Network (PAN) Europe** is a network of NGOs working to reduce the use of hazardous pesticides and have them replaced with ecologically sound alternatives. We work to eliminate dependency on chemical pesticides and to support safe sustainable pest control methods. Our network brings together 40 consumer, public health, and environmental organisations, and women's groups from across Europe.

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<sup>5</sup> E. Drakvik, and al., Statement on advancing the assessment of chemical mixtures and their risks for human health and the environment, Environment International, Volume 134, 2020, 105267, [ISSN 0160-4120](#).

<sup>6</sup> Cf. 5.

<sup>7</sup> Cf. 4.