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EDITORIAL

Paradigm shift in the risk assessment of cumulative effects of pesticide mixtures and multiple residues to humans and wildlife: German proposal for a new approach

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A paradigm shift is underway in the risk assessment of chemicals leaving behind the traditional "individual substance approach." This simplified approach has long been criticized for not adequately taking into consideration the well-known occurrence of chemical mixtures in relevant exposure matrices (foodstuff, environmental media) and thus ignoring the "added risk" resulting from multiple exposure and associated mixture toxicity. More recently, the adequacy of this approach was also questioned from the political arena in Europe (Council of the European Union 2009; European Commission 2012). As a consequence, several reviews of the state-of-the-science as well as opinions on the implementation of mixture risk assessment in chemicals regulation have been delivered. Further, the principal request for taking the risk of mixtures into due account has been introduced in recently updated European chemicals legislations, e.g. for plant protection products (PPP) and biocidal products (BP).

For PPP, regulation (EC) No 1107/2009 (European Commission 2009) requires in article 29 that "interaction between the active substance, safeners, synergists and co-formulants shall be taken into account" in the evaluation and authorization. This explicitly refers to marketed PPP, which are by origin technical mixtures containing one to several active substances plus typically several co-formulants. Consequently, the "mixture toxicity issue" for these technical mixtures is already mirrored in the standard data requirements for PPP. However, common agricultural practice comprises also the application of two or more PPP simultaneously (tank-mixtures prepared by the farmers directly before application) as well as the sequential application of several different PPP during the growing season (serial applications). Hence, there is well-justified concern for exposure of humans and non-target organisms towards "coincidental" pesticide (residue) mixtures resulting from common agricultural practice. Regarding human health risk assessment, a general and explicit request is laid down in the regulation (EC) No. 1107/2009, stating that PPP and their residues "[…] shall have no immediate or delayed harmful effect on human health, […], taking into account known cumulative and synergistic effects where the scientific methods accepted by the Authority to assess such effects are available; […]." With regard to the environmental risk assessment in the standard data requirements for PPP a quite similar sentence is included.

While there are clear regulatory requirements on adequately considering the risk from exposure to PPP (residue) mixtures, often the lack of agreed and sufficiently specific technical guidance is the major obstacle for a consistent and adequate implementation of mixture risk assessment under regulation

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(EC) No. 1107/2009. Under the lead of the European Food Safety Agency (EFSA), several activities have been undertaken in order to develop such guidance for human health risk assessment in recent times. Regarding environmental risk assessment, respective guidance was and is still successively incorporated in course of the on-going revision of the EFSA guidance documents. Clearly, the lack of agreed and sufficiently specific technical guidance harbors the threat of inconsistency in risk assessment and decision-making across EU member state authorities which would then severely collide with the newly established zonal authorization procedure. In the worst case, significant assessment uncertainties or inappropriate management decisions might result given the high biological effectiveness of plant protection products and their active substances.

Against this background, the regulatory authorities responsible for the risk assessment and risk management of PPP in Germany (Federal Office of Consumer Protection and Food Safety, BVL; Federal Office of Risk Assessment, BfR; Federal Environment Agency, UBA) developed this proposal for a new approach in order to provide a reflection on.

1. The current scientific understanding of the regulatory requirements,
2. The available options for implementation as well as,
3. The current practice in risk assessment and management in Germany.

This editorial intends to inform interested experts from industry, academia, regulatory bodies and NGOs on the current state-of-the-implementation of mixture risk assessment and risk management in Germany as a contribution for further discussion and harmonisation of this approach to implement this paradigm shift within the regulatory practice at the European level.

The BfR drafted a concept on how to take cumulative aspects into account in operator and consumer risk assessments in the regulatory context (Stein et al. 2014, in this issue pp. xxx). Application of this concept as part of the routine risk assessment for PPP and BP is envisaged as soon as suitable experience and an impact assessment has been gained in a testing phase. The concept uses dose-addition of individual active substances as the toxicological standard concept for cumulative risk assessment and proposes a tiered approach. It recommends to start with calculation of a hazard index (HI) for all relevant substances contained in the formulated product under consideration. Proceeding to higher tiers is currently foreseen if an unacceptable risk cannot be excluded. Refinements should consider both the toxicity and the exposure part of the cumulative risk assessment and will depend on availability of relevant data. BfR acknowledges the complexity of the refinement work in mixture risk assessment to be done. Due to the large number of approved pesticide formulations it is not feasible to test all the theoretically possible combination effects through repeated exposure as part of conventional animal experiments. For this reason, it is very important to develop and validate suitable model systems which can be used as screening test battery prior to any animal experiments.

The exposure assessment for operators, bystanders/residents and workers as well as the acute exposure assessment for consumers rely mainly on the active substances in a PPP or BP under consideration or on combinations of products for which simultaneous use is notified. Chronic consumer exposure assessment needs to take into account these substances, but also the residue background of other pesticides in food, which have to be derived from representative food monitoring programmes. A representative food monitoring database is currently being developed. The assessment requires the application of complex probabilistic methods. It is planned that BfR will review the chronic cumulative risk assessment for each active substance and each Cumulative Assessment Group (CAG) regularly as soon as all essential monitoring data are available. It is planned to carry out case studies on the impact on regulatory decisions.

For environmental risk assessment of PPP-mixtures two generic options are considered most adequate for the assessment of hazards and risks of pesticide mixtures by the UBA (Frische et al. 2014, see this issue pp. xxx): (1) whole mixture approach, i.e. direct experimental testing of the mixture of concern, just like a single substance and (2) component-based approach, i.e. calculating the expectable joint toxicity from toxicity data for individual mixture components by applying corresponding models, in particular those based on the reference models of concentration addition (CA) and independent action (IA). Particularly, CA is considered to provide a reasonable default (tier 1) assumption for such a predictive approach, with further added value within mixture risk assessment (e.g. counter-checking experimental mixture testing results, identifying potential drivers of mixture toxicity). The standard data made available during PPP authorization do generally allow for at least an initial mixture risk assessment. UBA

advocates the more extensive use of the component-based approach—at least if well justified—since these do allow for a mixture risk assessment without additional experimental testing, what is considered favorable both for animal welfare and economic reasons.

Regarding the risk management of PPP-mixtures including especially the setting of risk mitigation measures and the use of monitoring data for that purpose, standard data requirement and uniform principles exist as outlined above. Risk management decisions for human health were mainly based on an experimental data set for active substances supplemented by acute toxicity tests of the PPP and further information on co-formulates. In the environmental area testing of formulated products are well established although extent of data availability clearly depends on the respective assessment area. In principal those mixtures which were part of the application like for example specific tank mixes were taken into account when deciding upon the authorisation. In general tank mixes recommended later on for example by extension services were out ot the scope of the approval procedure. However, if clear evidence was available from monitoring studies or other sources that mixtures may pose a higher risk for human health or the environment as predicted additional data even for these tank mixes were required in approval procedures later on. Depending on the outcome of such specific assessments stronger risk mitigation measures were set for example to protect honey bees in case of mixtures of pyrethroids insecticides and strobilurine fungicides. With the new methods outlined in the accompanied papers of BfR and UBA more systematic approaches of identifying critical mixtures which may lead to clearly higher risks for human health or the environment are made available. For informed decision-making it would be important to predict the number of cases and height of additional risks and the impact on the functioning of the internal EU-market if the new rules will enter into force (impact assessment). Finally a proportionate way of dealing with the huge number of possible mixtures in the regulatory procedures should be developed avoiding a unsubstantiated increase of regulatory requirements.

The proposals outlined above are—inter alia—the result of discussions at the european level and from the regulatory point of view it is important coming to harmonised rules on the placing of products on the market at this level. Considering the vast amount of possible mixtures which may occur under real field conditions it might be good to integrate all fields of expertise into the discussion on mixture toxicity and cumulative risk assessment. Chemists formulating products and efficacy experts often know very well how to improve the biological performance of an active substance by combining them with other components (but lowering factors too). Taking this knowledge into account too should lead to an even more comprehensive evaluation of mixture toxicity.

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