

Plant protection products - high standards for risk assessment also in case of mixtures

Communication No. 025/2023 of 14 June 2023

People are exposed to a multitude of substances – this includes natural as well as man-made chemicals. In case of simultaneous co-exposure one speaks of exposure to so-called mixtures. In many instances this is harmless from a health point of view. That is, because either the substances, are not present in concentrations at which relevant health effects could occur, or because the body detoxifies them, rendering potentially dangerous substances harmless.

Mixtures become toxicologically relevant only in cases where effects of individual substances are amplified to an extent harmful to human health or when substances interact with each other in such a way that harmful effects can occur. This can occur regardless of the nature or origin of the mixture. Hence it does not matter whether the mixture in question was intentional or accidental, nor if it is composed of natural or “synthetic-chemical” substances.

However, deliberately produced mixtures, i.e. “intended” mixtures, have a predefined composition and are as such more straight forward to assess and evaluate than accidental mixtures. In its remit of consumer health protection, the German Federal Institute for Risk Assessment (BfR) also assesses and evaluates mixtures. Respective assessments are part of good toxicological practice in most regulatory silos for formulated mixtures or in cases where co-exposure to critical substances is foreseeable.

The assessment of so-called accidental mixtures is also taken into account, if known and relevant, but is a challenge due to the large number of possible substance combinations. The first task here is to identify the substances that can interact and for which the exposure is high enough for mixture toxicity to potentially occur. The BfR has developed a concept with suggestions for the identification of possible mixtures relevant to health:

<https://www.bfr.bund.de/cm/349/new-bfr-concept-for-identifying-chemical-combinations-with-potential-health-effects.pdf>.

Also taken into account according to the actual state of science are substances that can have effects at low doses. Data pending they will ideally be assessed following clear dose-response relationships as these principally also apply in mixtures. In cases where a clear dose-response relationship cannot be established the respective assessments usually follow a premise of exposure minimisation according to the ALARA principle (“As Low As Reasonably Achievable”). A special case are substances that fall under so-called regulatory cut-off criteria, i.e. they are undesirable due to their effects. Here, targeted use is usually ruled out with assessments of such substances, for example as contaminants, being correspondingly strict. Normally, these are all CMR substances of category 1, i.e. substances that are carcinogenic (carcinogenic), mutagenic (mutagenic) or toxic to reproduction (harmful to fertility and/or development), including respective endocrine disruptors.

Mixtures can have different effects depending on their mechanism of action. There are basically four ways in which substances can interact in a mixture. (1) They can have different effects independent of each other; (2) Their effect can add up (additive effect); (3) They can have a stronger effect together than the sum of the individual effects (synergistic effect); (4) They can weaken each other's effect (antagonistic effect). In the case of equal/similar effects,

www.bfr.bund.de

it is usually assumed that the effects will be additive. The prerequisite for this is that the ingested substances have the same mechanism of action and that they were ingested at the same time or in close temporal succession.

Various EU regulations already prescribe the consideration of cumulative and synergistic effects, e.g. EU Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market. Hence and in line with this requirement BfR developed a guideline for the cumulative assessment of plant protection products with the respective procedures being established since 2017. Essentially the respective assessments follow a levelled approach for the cumulative assessment of the various active substances, be it in plant protection products or in tank mixtures. By September 2020 workers and uninvolved third parties (residents and bystanders) were also included in these assessments. Studies on the effects of multiple residues from plant protection products give no reason to assume that the assessments currently carried out are not sufficiently conservative. Irrespective of this, the respective testing and assessment strategies are and were subject to continuous further development and ongoing research projects, several of which the BfR has been actively involved in. This includes EuroMix (<https://www.euromixproject.eu/>), PANORAMIX (<https://panoramix-h2020.eu>) and PARC (<https://www.eu-parc.eu/>).

At the same time, BfR also deals with other relevant questions, e.g. on the subject of endocrine-disrupting substances (so-called endocrine disruptors) for which the BfR has published FAQs (<https://www.bfr.bund.de/cm/349/questions-and-answers-on-endocrine-disruptors.pdf>) as well as an explanatory video (https://www.bfr.bund.de/en/hormones_and_endocrine_disruptors-307475.html).

Further Information on the BfR website on the subject of plant protection products

Questions and Answers on residues of plant protection products:

https://www.bfr.bund.de/en/questions_and_answers_on_residues_of_plant_protection_products_in_food-60852.html

Consumer safety and plant protection residues:

https://www.bfr.bund.de/en/consumer_safety_and_plant_protection_product_residues-197980.html

About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. The BfR advises the Federal Government and the States ('Laender') on questions of food, chemical and product safety. The BfR conducts its own research on topics that are closely linked to its assessment tasks.