Advice 05-2021 of the Scientific Committee established at the FASFC on the evaluation of hazard characterization of pesticide residues without toxicological health-based guidance value

Background & Terms of reference

When the maximum residue limit (MRL) of a pesticide is exceeded in a batch of food products, these products may not be placed on the Belgian or European market. In these cases, the Federal Agency for the Safety of the Food Chain (FASFC) always assesses the risk to determine the measures to be taken for protecting the consumer (*e.g.* recall of the products from consumers, notification in the 'Rapid Alert System for Food and Feed' - RASFF). The risk for the consumer is assessed by comparing the intake with the available toxicological health-based guidance values.

Several active substances of pesticides were re-evaluated at European level and their authorisation has not been renewed. Because a genotoxic or carcinogenic effect cannot be excluded for some of these substances, the European Food Safety Authority (EFSA) has not determined a health-based guidance value. This is the case, among others, for anthraquinone, chlorpyrifos, chlorpyrifos-methyl, dimethoate, omethoate and tricyclazole. Other substances, such as matrine, have never been authorised in Europe and their safety has not been assessed by EFSA either. To be able to assess the risk in case of non-compliance and to take proportionate measures to protect the consumer, the Scientific Committee has been asked for its opinion on the hazard characterization of these substances.

Method

This opinion is based on expert opinion and a review of the information available in scientific literature, in particular the assessment reports of the European Food Safety Authority EFSA, including 'benchmark dose' (BMD) modelling (using PROAST version 69.0) and *in silico* toxicological assessment (using Derek KB 2018 1.1, Sarah Nexus 3.0.0. and Vega 1.2.8 D).

Conclusions & Recommendations

When a toxicological health-based guidance value is not available or when there are indications of genotoxicity, the risk is often assessed based on the margin of exposure (MOE) approach. For substances of which the chemical structure is known but for which there is little or no relevant toxicity data, the toxicity can be assessed *in silico* (through mathematical models in computer simulations) and the 'Threshold of Toxicological Concern' (TTC) approach can be followed. In this regard, the Committee recommends the following approach for the hazard characterization of:

anthraquinone	LOAEL = 20 mg/kg bw per day (carcinogenicity)	MOE = 30,000
dimethoate	NOAEL = 0.1 mg/kg bw per day (developmental neurotoxicity)	MOE = 10,000
omethoate	idem as dimethoate	
matrine	TTC = 0.0025 µg/kg bw per day (genotoxicity)	
chlorpyrifos	LOAEL = 0.3 mg/kg bw per day (developmental neurotoxicity)	MOE = 30,000
chlorpyrifos-methyl	idem as chlorpyrifos	
tricyclazole	LOAEL = 4.2 mg/kg bw per day (liver tumours)	MOE = 30,000

Anthraquinone

Because there are still many uncertainties about the carcinogenic and genotoxic potential of anthraquinone and its metabolites, the Committee proposes to use a worst-case approach based on the lowest observed adverse effect level (LOAEL) of 20 mg/kg bodyweight (bw) per day from a carcinogenicity study in rats exposed to anthraquinone, and a MOE of 30,000. This MOE results from the margin of 10,000 that is applied as standard for genotoxic carcinogens and an additional uncertainty factor of 3 because a LOAEL and not a NOAEL (No Observed Adverse Effect Level' or dose at which no detectable adverse effects are observed) is considered as the reference point for calculating the margin of exposure. When the margin or ratio between this LOAEL and the exposure to anthraquinone is higher than 30,000, it can be assumed that the exposure is of low public health concern.

The Scientific Committee recommends revising the proposed approach for the hazard characterization of anthraquinone in future when, in addition to the active substance, the relevant metabolites are analysed and included in the residue definition for anthraquinone as well.

Dimethoate & Omethoate

Unless it would be demonstrated that genotoxic effects are excluded, it is recommended to follow the MOE approach for genotoxic substances for dimethoate and omethoate as well. The critical adverse effect for both dimethoate and omethoate is neurotoxicity, linked to the inhibition of acetylcholinesterase (AChE) activity. The most sensitive reference point that can be linked to this effect for dimethoate, is the NOAEL of 0.1 mg/kg bw per day from a developmental neurotoxicity study. The lowest reported NOAEL for neurotoxicity of omethoate is 0.2 mg/kg bw per day. Given that omethoate is a more potent AChE inhibitor than dimethoate, and considering the uncertainties regarding the toxicological data, the more conservative NOAEL of 0.1 mg/kg bw per day is therefore taken as reference point for omethoate as well. When the margin between this NOAEL and the exposure to dimethoate or omethoate is below 10,000, the exposure should be regarded as a health concern.

Matrine

No toxicological data were found in the scientific literature on which to base the hazard characterization of matrine. Based on the structure-biological activity relationship and mathematical relationships between biological activities and measurable physicochemical parameters (i.e. (Q)SAR or '(Quantitative) Structure-Activity Relationship'), a genotoxic potential cannot be excluded. The Committee therefore proposes applying the Threshold of Toxicological Concern (TTC) of 0.0025 µg/kg bw per day for genotoxic substances. The TTC is a threshold value above which exposure is of toxicological concern. If exposure is inferior to this TTC, the likelihood of adverse health effects is assumed to be low.

Chlorpyrifos & Chlorpyrifos-methyl

Due to unclarity on the genotoxic potential of chlorpyrifos and chlorpyrifos-methyl, no health-based guidance values can be established. For chlorpyrifos, the LOAEL of 0.3 mg/kg bw per day for developmental neurotoxicity is considered as reference point. The available results on developmental neurotoxicity of chlorpyrifos-methyl appear to be insufficient to derive a reference point. Therefore and as a conservative approach, the LOAEL of 0.3 mg/kg bw per day from the chlorpyrifos study is applied to chlorpyrifos-methyl. Applying an additional uncertainty factor of 3 because the reference point is a LOAEL and not a NOAEL, results in an MOE of 30,000. When the margin between the LOAEL and the exposure to chlorpyrifos or chlorpyrifos-methyl is lower than 30,000, the exposure should be considered of concern.

Tricyclazole

Although the opinion of experts on the genotoxic potential of tricyclazole is divided, it is recommended to incorporate the necessary safety into the risk assessment. As a reference point, the LOAEL of 4.2 mg/kg bw per day, which is the lowest dose tested in a long-term toxicity and carcinogenicity study of tricyclazole, is proposed. If the margin between this LOAEL and the exposure is below 30,000 (i.e. the MOE), the exposure should be considered of concern. When new information should indicate that tricyclazole is not genotoxic, an 'Acute Reference Dose' (ARfD) of 0.05 mg/kg bw and an 'Acceptable Daily Intake' (ADI) of 0.0042 mg/kg bw per day may be considered as health-based guidance values.

The toxicological endpoints proposed in the opinion are subject to uncertainties due to various gaps in the available toxicological data and studies. These uncertainties are addressed by adopting a conservative approach. Clearly, these toxicological endpoints will have to be revised if new information on the adverse effects of these substances would become available.

Finally, it should be noted that the risk assessment of pesticides for which the level in a food product exceeds the MRL, by default, is based on an acute exposure estimation ('Provisional Short-Term Intake' or PSTI). The approaches proposed for the substances discussed in this opinion are based on a possible carcinogenic and/or genotoxic potential of these substances or on the TTC approach. Carcinogenic and genotoxic effects are usually associated with long-term (chronic) exposure and the TTC approach also assumes long-term exposure. Consequently by considering the acute rather than the chronic exposure, an additional safety is built into the risk assessment.

The full text is available on this website in dutch and in french.