

## SCIENTIFIC OPINION

# Scientific Opinion on Risk Assessment for a Selected Group of Pesticides from the Triazole Group to Test Possible Methodologies to Assess Cumulative Effects from Exposure through Food from these Pesticides on Human Health<sup>1</sup>

EFSA Panel on Plant Protection Products and their Residues (PPR Panel)<sup>2, 3</sup>

European Food Safety Authority (EFSA), Parma, Italy

### SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Plant Protection Products and their Residues (PPR Panel) to deliver a scientific opinion on risk assessment for a selected group of pesticides from the triazole group to test possible methodologies to assess cumulative effects from exposure through food from these pesticides on human health.

This opinion was preceded by an opinion in which the PPR Panel evaluated existing methodologies on cumulative dietary risk assessment and recommended that a tiered approach should be adopted both for toxicological evaluation and exposure estimations. It was decided to test the proposed approach by preparing a worked example of a cumulative dietary risk assessment for the group of triazoles.

First, the Panel used the proposed criteria by which to group compounds for such an assessment, i.e. to create a cumulative assessment group (CAG). The grouping was based on general criteria like chemical structure, mechanism of pesticidal action and common toxic effect, or more refined criteria like mode or mechanism of action. Seven triazoles – bitertanol, cyproconazole, diniconazole, epoxiconazole, flusilazole, propiconazole and triadimefon - were identified to produce an acute effect, cranio-facial malformations, possibly via a common mechanism of toxicity and were put together in an acute CAG. Hepatotoxicity was selected as the endpoint for the chronic assessments in this case study. The CAG for chronic assessment (hepatotoxicity) was derived by taking the 7 triazoles from the acute group plus adding 4 other hepatotoxic triazoles for which there were extensive residue monitoring data (as of January 2008). This was done for pragmatic reasons to give a chronic CAG supported by a useable dataset. The resulting CAG comprised: bitertanol, cyproconazole, difenoconazole, diniconazole, epoxiconazole, flusilazole, myclobutanil, propiconazole, tebuconazole, triadimefon and triadimenol.

1 On request of EFSA, Question No EFSA-Q-2007-183, adopted on 19 June 2009.

2 Panel members: Damia Barcelo Culleres, Jos Boesten, Claudia Bolognesi, Alan Boobis, Arne Büchert, Ettore Capri, David Coggon, Anthony Hardy, Andy Hart, Herbert Koepp, Matthias Liess, Robert Luttik, Otto Meyer, Stella Michaelidou-Canna, Mark Montforts, Angelo Moretto, Markus Müller, Bernadette Ossendorp, Walter Steurbaut, Maria Tasheva, Christiane Vleminckx. Correspondence: ppr@efsa.europa.eu

3 This opinion is based on major contributions from: Mr. Arne Büchert, Ms. Bernadette Ossendorp, Ms. Maria Tasheva, Ms Ursula Banasiak, Ms. Claudia Bolognesi, Mr. Alan Boobis, Mr David Coggon, Mr. Ian Dewhurst, Mr. Paul Hamey, Mr. Andy Hart, Mr. Otto Meyer, Ms. Stella Michaelidou-Canna, Mr. David Miller, Mr. Angelo Moretto, Mr. Markus Müller, Mr. Jacob van Klaveren, Ms. Christiane Vleminckx, Mr. Doug Wolf.

For citation purposes: EFSA Panel on Plant Protection Products and their Residues (PPR Panel) Scientific Opinion on risk assessment for a selected group of pesticides from the triazole group to test possible methodologies to assess cumulative effects from exposure through food from these pesticides on human health on request of EFSA. EFSA Journal 2009; 7(9):1167. [3 pp.]. doi:10.2903/j.efsa.2009.1167. Available online: [www.efsa.europa.eu](http://www.efsa.europa.eu)

The PPR Panel used the following tiers for the hazard characterisation 1) ADI, ARfD; 2) “ADI”, “ARfD”, adjusted for the common endpoint; 3a) NOAEL for the common endpoint; 3b) BMD for the common endpoint.

To assess exposure, deterministic models based on average (chronic) or 97.5 percentile (acute) consumers were used for tiers 1 to 3 and probabilistic modelling for tier 4.

Four scenarios were considered to be relevant. These were (i) actual exposure (i.e. from the patterns of usage that actually occur in practice), during an acute (i.e. 24 hours) time span; (ii) actual exposure extrapolated to a chronic (i.e. lifetime) time span; (iii) acute (i.e. 24 hours) exposure relevant for MRL-setting (i.e. a theoretical exposure where the residue of the compound/commodity combination under evaluation is at the level of the MRL); and (iv) chronic (i.e. lifetime) exposure relevant for MRL-setting assessed at the level of the STMR.

In summary, risk assessment was performed for each of the four scenarios by calculating the Hazard Index (HI), adjusted HI (with several tiers of refinement on the exposure side) and using the Relative Potency Factor (RPF) method, where the RPF method was applied using either NOAELs or BMDs as the Reference Point (RfP) and exposure estimates were used that were derived either deterministically or probabilistically.

The worked example proved to be very valuable in testing the methodology and identifying the necessary next steps before its routine application by EFSA could be recommended.

The PPR Panel concluded that the previously proposed tiered approach could be simplified by:

- starting with a CAG as refined as the data would allow and using the same CAG in all steps of the assessment;
- restricting each exposure scenario to two tiers, one deterministic and one probabilistic tier.

The Panel noted that when assessment of a CAG based on relatively broad criteria fails to give adequate reassurance (due to the absence of information on mode or mechanism of action for the common toxicological effect) this may serve as a trigger for further research to enable the assessment to be completed.

The establishment of relevant CAGs is the starting point for all cumulative risk assessments. Consensus should be reached at an international level on the criteria and compounds that should be used to create a CAG, to avoid differences between national cumulative risk assessments.

An important issue is that a first tier should be more conservative compared to the next tiers. In itself, the hazard assessment tiers are clear and could be performed for any CAG.

However, the PPR Panel concluded that there are still several issues that need to be addressed before the cumulative exposure assessment methodology can be applied routinely. The principal reasons for this are that the level of protection provided by the deterministic exposure assessments is uncertain and that some details of the probabilistic methodology require further work (see section 6.4). Some indication of the level of protection of the deterministic approach is provided by comparison with the results of the probabilistic assessment for triazoles, but these are themselves uncertain and the outcome of the comparison cannot be generalized to other CAGs.

Further work is needed to address some issues that were encountered. For instance, the method of calculation of the so-called background exposure in the deterministic tiers is open to question, as is the issue of how to handle non-detects in both the deterministic and probabilistic approaches.

The Panel is currently developing guidance for probabilistic modeling of exposures to single pesticides. As part of this work, the Panel is considering methodological issues that also affect the use of probabilistic approaches for cumulative assessments. The Panel therefore recommends that this guidance should be considered when further developing probabilistic approaches for cumulative risk assessment. When the probabilistic approaches are considered sufficiently robust, they can be used to further calibrate the level of protection provided by the proposed deterministic approaches and if necessary adjust it (e.g. by modifying the method for calculating background exposure).

Overall, the PPR Panel concludes that although a tiered approach is an appropriate way to address cumulative dietary risk assessment it cannot yet be applied on a routine basis. First, the following issues should be resolved:

1. the basis for and establishment of relevant CAGs, on a European level;
2. confirmation that both the deterministic and probabilistic approaches for cumulative exposure assessment provide appropriate levels of protection;
3. completion of further guidance on appropriate methodologies for exposure assessment.

It is important to note that the present exercise is not to be taken as a definitive EU risk assessment of the combined triazole group, but rather as a worked example testing the methodology proposed in the previous opinion.

**KEY WORDS:**

Cumulative risk assessment, dietary exposure, MRL, residue monitoring, tiered approach, cumulative assessment group, triazole chronic exposures, acute exposures.