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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[1]

EFSA Panel on Plant Protection Products and their Residues (PPR Panel)[2, 3]

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ABSTRACT

Regulation EC No. 396/2005 from the European Parliament and the Council has required since September 2008 that cumulative and synergistic effects of pesticides be considered when Maximum Residue Levels (MRLs) are adopted. On 15 April 2008, the PPR Panel adopted an opinion on the suitability of existing methodologies and proposed a tiered approach for assessment of the cumulative effects of pesticides. As a second stage of its work in this area, the PPR Panel carried out a cumulative risk assessment for triazole fungicides to test the methods that had been proposed. This exercise applied the tiered approach in different scenarios of relevance for risk management in pre- and post-registration conditions, for both acute and chronic cumulative effects. The PPR Panel describes in this opinion progressive steps of refinement in cumulative risk assessment: (i) establishment of a Cumulative Assessment Group (CAG) through a careful analysis of the specific toxicological effects common to triazole pesticides and their underlying biochemical mechanisms, (ii) refinement of the hazard characterisation, using in successive tiers, regulatory reference values, reference values based on the common specific toxicological effects and benchmark dose modelling, and (iii) refinement of the cumulative exposure assessment making use of deterministic and probabilistic methodologies in successive tiers. Based on the lessons learned from this exercise, the PPR Panel proposes a simplification of the overall tiered approach. The CAG should be as refined as the data allow at an early stage, and exposure assessments should ideally be restricted to one deterministic and one probabilistic tier. 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. The PPR Panel identified the following issues that should first be resolved: the basis for and establishment of CAGs on a European level, definition and

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agreement on desired levels of protection, improvement of the robustness of methodologies of cumulative exposure assessment and development of guidance on their appropriate use.

KEY WORDS

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

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 throughout 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 to group the compounds for such an assessment i.e. to create a cumulative assessment group (CAG).The grouping can be 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 usable dataset. The resulting CAG comprised: bitertanol, cyproconazole, difenoconazole, diniconazole, epoxiconazole, flusilazole, myclobutanil, propiconazole, tebuconazole, triadimefon and triadimenol

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 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 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, due the absence of information on mode or mechanism of action for the common toxicological effect, fails to give adequate reassurance, 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 modelling 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.

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BACKGROUND AS PROVIDED BY EFSA

Regulation (EC) No. 396/2005 on maximum residue levels (MRLs) emphasises the importance "to carry out further work to develop a methodology to take into account cumulative and synergistic effects of pesticides". In fact, the European Parliament itself has – at the time of the adoption of the Regulation - required that such a methodology be developed and applied as soon as possible to assess the safety of MRLs. Consequently, the PPR Panel, itself, had tasked to evaluate the suitability of existing methodologies and, if appropriate, refine these and/or identify new approaches to assess possible cumulative and synergistic risks from pesticides to human health, for the purpose of setting MRLs for pesticides within the framework of Regulation (EC) No. 396/2005. For more information, refer to background and terms of references for its earlier opinion. (EFSA-Q-2006-160).

While an opinion on the theoretical aspects of developing such methodologies will provide the background, the PPR Panel considered it necessary also to test its proposals for methodologies using a set of pesticides that share a common mode of action. A number of similar risk assessments have been carried out previously by different risk assessment bodies, notably on organophosphorus compounds, chloroacetanilides, triazines and N-methyl carbamates. In order to avoid duplication of this work, and to address a group of compounds of considerable interest in the context of cumulative risk assessment, the PPR Panel agreed to identify a set of pesticides from the triazole group with a common mode of action (i.e. involving the same key events leading to an adverse health effect following interaction of the compound with its biological target[s]) to be used for testing the reliability and relevance of the methodology proposed and to refine recommendations made in the context of the earlier opinion of the PPR Panel "to evaluate the suitability of existing methodologies. If appropriate, the identification of new approaches will be applied to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) No. 396/2005". It is not intended to provide a complete assessment of cumulative risks to human health for triazole compounds.

TERMS OF REFERENCE AS PROVIDED BY EFSA

The PPR Panel is requested to carry out a 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

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ASSESSMENT

1. Introduction

In April 2008, the PPR Panel adopted an Opinion in which methodology to address possible cumulative and synergistic effects of pesticides was reviewed (EFSA, 2008a). In that Opinion, the Panel made specific proposals for methodological approaches to use, but recommended that, prior to adoption of the methodology, a worked case study should be undertaken by the Panel. This Opinion reports the results of such a case study in which the proposed methodology was applied to the cumulative risk assessment of a group of triazole pesticides.

1.1. Rationale for the proposed tiered approach to cumulative risk assessment

The PPR Panel has proposed criteria by which to group compounds for such an assessment , i.e. to create a cumulative assessment group (CAG) highlighting the possibility of different levels of refinement in a step-wise approach. The grouping can be based on general criteria like chemical structure, mechanism of pesticidal action and common toxic effect, or more refined criteria like toxic mode or mechanism of action.

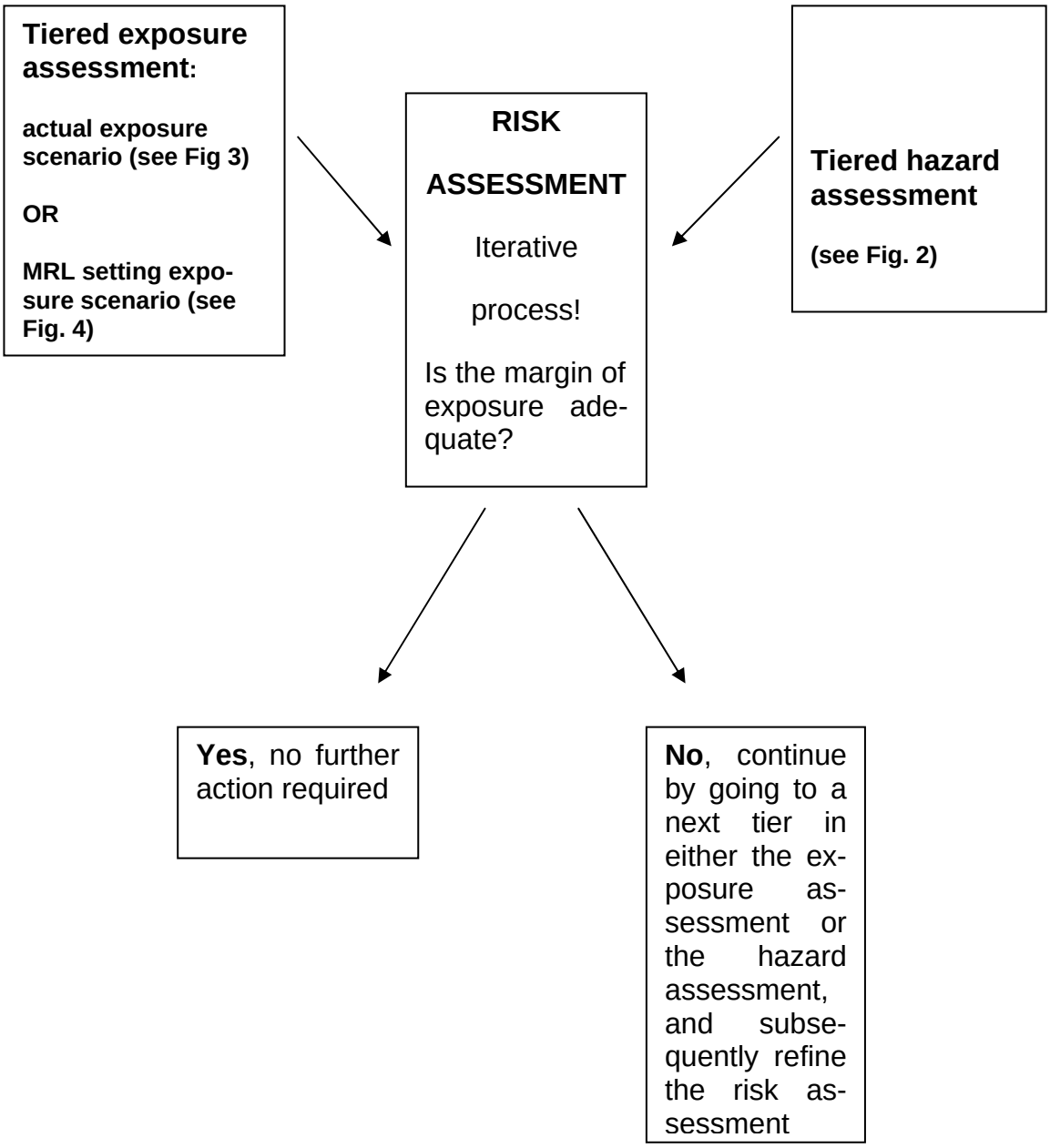
Furthermore, the PPR Panel proposed in its previous Opinion that a tiered approach for both toxicological evaluation and intake estimation be adopted in order to make the most efficient use of the available resources. The approach is visualized in Figure 1. The risk assessor should start with a combination of lower tier methods (the choice of starting point depending on the data that are readily available). If a lower tier assessment does not give adequate reassurance of safety, then the risk assessor should progress to a higher tier method, jumping by one or more steps for either or both of toxicological and exposure assessment, and if necessary proceeding eventually to an estimate of risk based on the use of PBPK modelling for establishing reference points, with probabilistic assessment of exposure based on individuals rather than person-days.

It should be noted that it is crucial for any tiered approach that lower tier assessments are sufficiently conservative. This ensures that, if a lower tier deterministic assessment (e.g. based on the hazard index) proves satisfactory on the basis of criteria agreed with risk managers, the risk manager can be assured that the margin of exposure is at least that which would normally be required for an individual pesticide. If a lower tier assessment does not meet the criteria for acceptability, this does not necessarily imply that there is unacceptable risk and/since a more refined assessment may demonstrate that exposure is not of concern.

With respect to cumulative exposure assessment, 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; actual exposure during 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 assessed at the level of the STMR (Supervised Trial Median Residue).

The actual exposure assessments provide a means to check whether the actual use of pesticides is acceptable because they investigate the actual exposure based on monitoring results and therefore provide an estimate on the percentage of the population that may be (or has been) at risk. The MRL-setting assessments, on the other hand, focus on the level of the MRL itself and try to ascertain whether consuming a commodity containing a residue at the level of the established or proposed MRL is acceptable.

Figure 1. Proposed cumulative risk assessment process, using a tiered approach for exposure and hazard assessment (reproduced from EFSA, 2008)



In the current PPR Panel Opinion, a worked example of the proposed methodology has been developed for the group of triazole fungicides. The results and experience gained have been used to refine the methodology as necessary.

It is important to note that the present exercise should not be considered as the definitive EU risk assessment of the combined triazole group, but rather as a worked example which illustrates and tests the methodology. The goal of this project was to address as many tiers of the tiered approaches as possible, and not necessarily to be comprehensive or complete. For instance, the common metabolites 1,2,4-triazole (free triazole), triazole alanine and triazole acetic acid were not considered in the assessment;

the number of compounds included in the CAG for chronic toxicity was limited for pragmatic reasons. A major dimension of the exercise was to evaluate potential methods for conducting cumulative risk assessments and (1) determine the extent to which necessary information and data may or may not be available; and (2) make prioritized recommendations and identify additional data needs.

1.2. General approach to hazard identification and characterisation

In its earlier Opinion, the Panel discussed the different ways in which a group of compounds could produce a combined effect: dose-addition, response-addition and interaction (e.g. inhibition, synergy). The Panel concluded that unless there is evidence to the contrary, residues of pesticides sharing a mode of action, when used as approved, could be assumed to act in combination by dose-addition (see EFSA, 2008a for supporting evidence).

Therefore, cumulative risk assessment starts with the identification of a candidate group of compounds, called a cumulative assessment group (CAG), that is assumed, by default, to cause a common toxic effect by a common mode of action, and hence potentially to exhibit dose addition. Construction of a suitable CAG, the assessment of which will provide valuable information of value to risk managers, is a complex process, requiring considerable toxicological expertise. In principle, all compounds acting by the common mechanism should be included in a cumulative risk assessment, whatever their use or indeed, their chemical structure. This would include not only pesticides, but biocides, veterinary and human medicines, consumer products, natural chemicals, e.g. those in the diet, food additives, industrial chemicals and environmental contaminants. However, this would be possible only if detailed information on mode or mechanism of action were available on these compounds, so that there was confidence that they were likely to act on the same molecular target, or on related targets such that there would be dose addition. Otherwise, the assessment would be so conservative that the outcome would not be of any value to risk managers. For the purpose of the current exercise, selection was restricted to pesticidal active substances in use in Europe.

The grouping is based on one or more of the following criteria:

- Chemical structure – toxicophores, based on core molecule structure, specific functional groups or their metabolic precursors;
- Mechanism of pesticidal action – the mechanism of mammalian toxicity of a number of pesticides is similar to that responsible for their activity against target organisms;
- General mode/mechanism of mammalian toxicity – this is based on a relatively broad consideration of mode of action and not a detailed evaluation of key events;
- A specific toxic effect – it is possible that similar toxic effects are caused by structurally unrelated compounds via the same mode of action (MOA). Non-specific effects such as changes in body weight or death should not be used as a basis for membership of a CAG.

A CAG identified as above can be further refined by a number of steps. These start with definitive identification of those compounds that cause the same toxic effect, on the basis of both site and nature of toxicity. Compounds not causing the common effect are excluded from further consideration in the combined assessment. Subsequent refinement can be achieved by determining the mode/mechanism of action (MOA) for the toxic effect caused by each substance by consideration of the key events involved. In the absence of this type of detailed information, it may however be sufficient to group compounds for a cumulative assessment on the basis of less refined criteria (e.g. target organ toxicity).

The final selection in the CAG includes those compounds presenting sufficient hazard potential to warrant inclusion in the quantitative estimates of risk. As a next step, compounds can be excluded from the exposure assessment when it is expected that exposure to those compounds will be negligible.

Initially, the usual reference values as determined for each compound during the evaluation under EC/91/414, ADI (Acceptable Daily Intake) and ARfD (Acute Reference Dose), can be used for cumulative risk assessment. These are derived by dividing the NOAEL (No Observed Adverse Effect Level) for the most sensitive toxicological end-point by an appropriate uncertainty factor (UF) for inter- and intra-species differences. Usually this UF is 100 (=10x10). In addition, compound-specific UFs may be applied. However, such NOAELs for the different compounds in the CAG may not be based on the same toxic effect. A first step of refinement is therefore to identify the NOAELs for the common toxic effect. Another choice is whether to apply individual UFs, or to use one UF for the whole group, applied to the combined exposure. Further refinement can be achieved by using BMD (Benchmark Dose) values instead of NOAELs (EFSA, 2009).

1.3. General approach to exposure assessments

Ideally, all exposure by all routes should be considered in a cumulative risk assessment. However, as discussed in its previous Opinion (EFSA, 2008a), it is currently not feasible to undertake multi-route (i.e. so-called aggregate) assessments of pesticides on an EU-wide scale. Hence, for the purposes of this exercise, exposure assessment was limited to residues of pesticides in food.

To calculate the dietary exposure to pesticide residues, data are needed both on consumption patterns for the population of interest, and on residue data representing the relevant scenario. The requirements and availability of these data are described in detail in the previous PPR Panel Opinion on cumulative risk assessment (EFSA, 2008a).

Exposure assessment calculations can be performed either deterministically ("point estimates", in essence: multiplying a residue value by a single consumption value) or probabilistically (in essence: multiplying a distribution of residue values with a distribution of consumption values). In theory, when the same assumptions are used for both deterministic and probabilistic intake calculations, the outcomes should be comparable. For acute intake calculations, where the aim is to calculate a high exposure, the outcome of the point estimate should be at the high end of the intake distribution as calculated by the probabilistic method. For chronic intake calculations, where the aim is to calculate a mean exposure[4], the outcome of the point estimate should be at the mean of the intake distribution as calculated by the probabilistic method. The main advantage of a deterministic method is that it is relatively easy to perform and does not require sophisticated software. The main advantage of a probabilistic method is that it takes into account the full range of exposures and their associated probabilities. The PPR Panel stated in its previous opinion that, in general, a refined cumulative exposure assessment (including multiple commodities and multiple pesticides belonging to a CAG) cannot be done without using probabilistic methods. However, it was concluded that for a single commodity containing multiple residues of pesticides belonging to a CAG, a deterministic assessment can be done based on the I(N)ESTI (International (National) Estimate of Short Term Intake) and TMDI (Theoretical Maximum Daily Intake)/I(N)EDI (International (National) Estimated Daily Intake)equations as used for assessments for individual chemicals. As the first steps in the tiered risk assessment process should be as simple as possible, deterministic intake calculations were performed in the course of the worked example.

It was proposed in the previous opinion that in estimating the actual cumulative exposure scenarios (both acute and chronic), residue levels from monitoring programmes should be used in the assessment for all commodity/pesticide combinations. Furthermore, the group of consumers considered in such an 'actual' assessment should be the total population of interest (e.g. general population or children of a

4 In the methodology currently used for EU MRL-setting, the following is stated: For the long-term exposure assessment, consumption data derived from the whole population or sub-groups of the population as a mean value should be considered. The mean consumption figures are preferred as they better reflect the food consumption habits and not the day-to-day variation, which allows for a comparison of the relevant toxicological threshold (i.e. the ADI), which is based on intake over a lifetime (EFSA 2007a). However, the aim could also be to assess the exposure of consumers with a high consumption of certain foods (see e.g. WHO, 2008). This needs to be further discussed within the context of cumulative risk assessment, see also chapters 6 and 7.

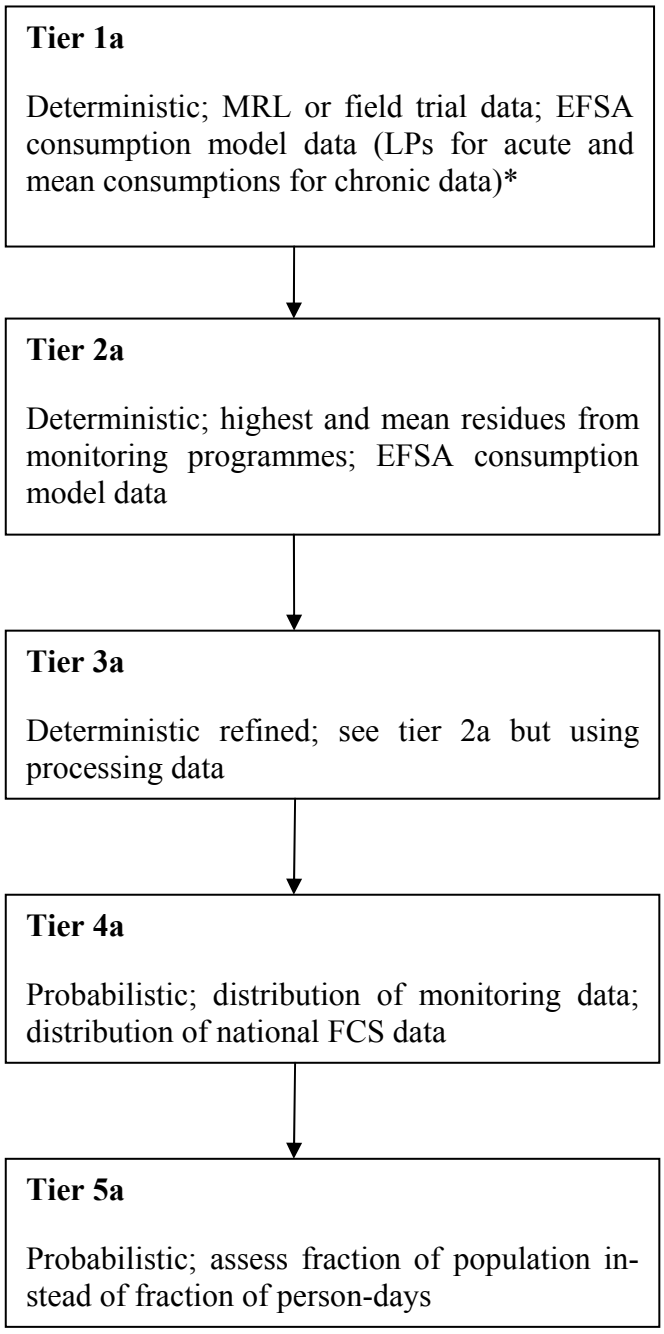
specific age group) who, by definition, includes non-consumers of a certain commodity. This is because, for an actual exposure assessment, there is no specific emphasis on a particular commodity for which the MRL is proposed to be set, but rather an interest in obtaining an overall picture of the usual (or background) pesticide exposure of consumers.

In the acute cumulative MRL-setting scenario, on the other hand, residues at the level of the MRL should be taken into account only for the commodity/pesticide combination for which the MRL is to be set. Furthermore, the group of consumers considered should only be those who consume the commodity of interest. This type of selection is also called the 'eaters only' or 'consumers only' approach and contrasts with the approach for estimating the actual exposure for which all individuals are included. For all other commodity/pesticide combinations in the assessment, background levels (e.g., from monitoring programmes) should be used.

With regard to chronic cumulative risk assessment for MRL-setting purposes, it was noted that while for individual chemicals, a worst-case assumption is that consumption could involve commodities with residues present at the MRL for all commodities of interest over a lifetime, this assumption would be very unrealistic for a cumulative assessment. It was concluded that as a first tier, an assessment combining lifetime exposure at the STMR for the specific commodity/pesticide combination undergoing evaluation with background exposure (as derived from monitoring programmes) for all other commodities/pesticides would be a more reasonable assessment.

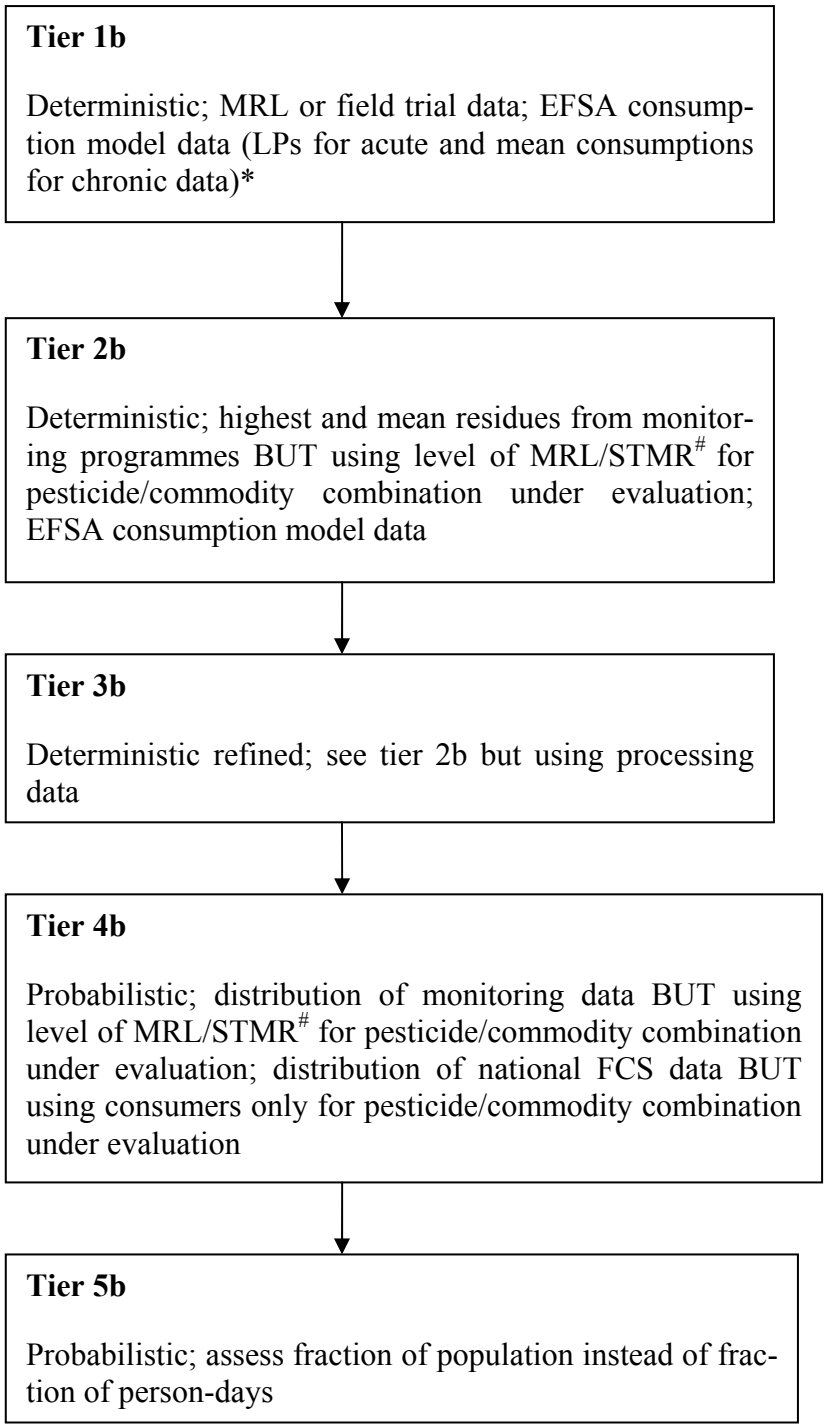
Refinement steps in the exposure assessment could be achieved by moving from deterministic to probabilistic methods, and by incorporating data on the effect of processing on the nature and amount of the residue. See Figures 2 and 3 for the proposed tiered exposure assessments for actual exposure and MRL setting scenarios respectively.

Figure 2. Tiered exposure assessment, actual exposure scenarios (reproduced from EFSA 2008)



* EFSA consumption model data when performing a European assessment, on the national level national consumption data may be used

Figure 3. Tiered exposure assessment, MRL setting exposure scenarios (reproduced from EFSA 2008)



* EFSA consumption model data when performing a European assessment, on the national level national consumption data may be used

\# Use MRL or STMR depending on scenario (acute vs. chronic)

1.4. General approach to cumulative risk assessment

In the previous PPR Panel Opinion on cumulative risk assessment, several methods for cumulating the toxicity of compounds in a CAG (i.e. performing a cumulative risk assessment) were described. The methods use the same underlying data, but express the information differently. The PPR Panel concluded that the most useful methods were in increasing levels of complexity and refinement, the hazard index (HI), the reference point index (RfPI), the relative potency factor method (RPF) and finally a combination of physiologically-based toxicokinetic (PBTK) modelling for establishing reference values, with probabilistic assessment of exposure based on individuals rather than person-days. The Panel noted that the cumulative risk index (CRI) and the combined margin of exposure (MOE) are reciprocally related to the HI and the RfPI, respectively. As such, they were not included in the tiered approach. The main reason for including the HI and the RfPI and not the CRI and the combined MOE is that the latter two are conceptually more difficult to understand. It is, however, possible that the combined MOE is simpler to communicate to the public, see Chapter 6 for further discussion.

The HI is the sum of the ratios between exposure and the reference value (RV) (i.e. acceptable daily intake, ADI, or acute reference dose, ARfD) for each component (hazard quotient, HQ). A ratio of less than 1 means that the combined risk is considered acceptable. The HI is transparent and understandable, since it relates directly to the RV, which is a long-used and well-understood index of acceptable risk. In addition, since RVs are readily available, application of this methodology is (relatively) rapid and simple and it can serve as a useful screening method. It should be noted that RVs are obtained by application of an UF that may incorporate policy (e.g. default extra UF for children or severity of effect) and scientific (e.g. on the quality of the database that might not be directly related to the relevant toxic effect) judgments. As such, it does not necessarily represent a true measure of relative toxicological potency of the different compounds. In addition, use of RVs based on a mix of animal and human data is equivalent to comparing potency determined in different species. Whilst this is possible, it does introduce an inconsistency into the process which will be reflected in differences in the outcome when compared to that obtained using some of the other approaches described below. This issue is addressed further in Section 6.3. Refinement of the HI (adjusted HI) can be performed when the RV of a certain compound is based on an effect that is not the group effect (common toxic effect) or the assessment factor applied includes adjustments not related to the endpoint of concern.

The Reference Point Index (RfPI) expresses the sum of exposure to each pesticide as a fraction of their respective RfPs for the relevant effect. It is intuitively more straightforward and mathematically simpler than other methods. It is also more transparent because UFs are not used prior to calculating the RfP. A single group UF can be applied as the last step in the process. However, the use of the RfPI does not allow the application of chemical specific adjustment factors (CSAFs) (e.g. for interspecies differences), including those associated with the availability of data in humans, unless this is done earlier in the process, if needed. For these reasons, study design should preferably be comparable for all compounds.

The Relative Potency Factor (RPF) approach is somewhat different from the others in that it relies on expressing the different potencies of all members of the group relative to that of an index compound (IC). To estimate the cumulative risk of the CAG the different compound potencies must be put on a common scale to normalize the exposure to the compounds. The steps in the Relative Potency Factor (RPF) approach are the following:

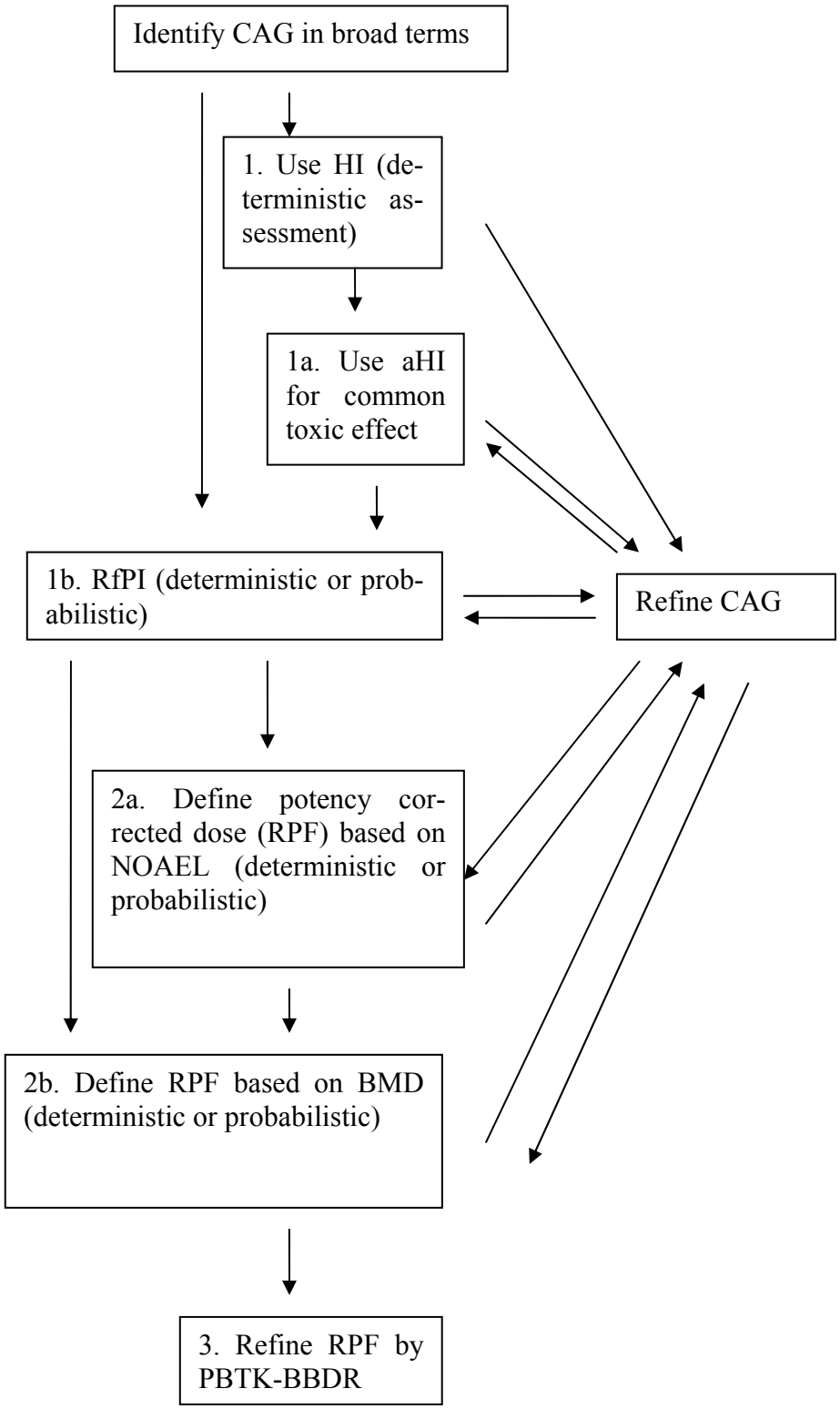
- Determination of the toxic potency of each compound – using either the NOAEL/LOAEL or BMD for the common effect.
- Selection of the IC to be used for standardizing the toxic potencies of each CAG member.
- Calculation of RPFs for each CAG member.

The toxicological activity of the mixture is then determined by the sum of the potency-normalised exposures to each CAG member and expressed as IC equivalents. This total equivalent exposure is compared

to the RV of the IC. If lower than the RV of the IC, the combined risk from exposure to the compounds in the mixture is considered acceptable.

In the previous opinion, the measures of cumulative risk (HI, RfPI and RPF) were presented in a scheme called 'Tiered hazard assessment'. This was due to the fact that refinements in this scheme were solely referred to refinements in the toxicological reference values, not to the exposure estimations. However, since the HI and RfPI combine information on exposure as well as hazard, they should more properly be referred to as measures of risk. See figure 4.

Figure 4. Tiered hazard/risk assessment (reproduced from EFSA 2008)



BBDR=Biologically-based dose-response modelling

1.5. Summary of scope of the opinion

Following the PPR Panel Opinion on methodologies for cumulative risk assessment of pesticide residues in food (EFSA, 2008a), in the current PPR Panel Opinion, a worked example of the proposed methodology was developed for the group of triazole fungicides. The results and experience gained are described and used to refine the methodology as necessary.

The PPR Panel used the following tiers for the hazard characterisation: A) ADI, ARfD; B) "ADI", "ARfD", adjusted for the common endpoint; C) NOAEL for the common endpoint; D) BMD for the common endpoint. On the exposure side, 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. This means, in combination, that risk assessment was performed by the HI, adjusted HI (with several tiers of refinement on the exposure side), and RPF methods, where the RPF method was applied using either NOAEL or BMD as RfPs, and using exposure estimates that were either derived deterministically or probabilistically. See table 1. An important issue is that a first tier should be more conservative compared to subsequent tiers. One of the aims of this opinion was to test and compare this for the various tiers.

Table 1. Overview of worked example of tiered cumulative risk assessment. Please note that the scheme has to be worked through for each of the identified exposure scenarios: actual_acute, actual_chronic, MRL-setting_acute and MRL-setting_chronic.

Hazard tiers		Exposure tiers			
		1	**2**	**3**	**4**
		Deterministic, MRL	**Deterministic monitoring**	**Deterministic + processing**	**Probabilistic**
A	**ADI, ARfD**	HI			
B	**Adjusted* ADI, ARfD**	adjusted HI	adjusted HI	adjusted HI	
C	**NOAEL***			RPF	
D	**BMD***			RPF	RPF

* for common effect

1.6. Structure of the opinion

Chapters 2 to 5 present the results of the triazole exercise, more specifically the hazard characterisation and refinement of the CAG are discussed in Chapter 2, the exposure assessments are presented in Chapter 3, and the final risk assessments -presented as case studies- appear in Chapter 4. Chapter 5 deals with the uncertainties in the risk assessment, and offers suggestions on how these uncertainties can most appropriately be communicated. Next, in Chapter 6 the 'lessons learned' from the triazole exercise are summarized and the methodology proposed by the PPR Panel in the previous Opinion is evaluated. Where necessary, the proposed methodology is adapted. The final chapter, Chapter 7 discusses conclusions and recommendations.

2. Hazard identification and characterisation of triazoles

2.1. Determination of the cumulative assessment group (CAG)

2.1.1. Common toxicophore

As discussed in the Background, it was agreed that the triazoles would be used as the CAG in this Opinion. The triazoles comprise a large number of pesticides. The Panel focussed on fungicides in use in Europe for crop protection. They share the presence of a single triazole ring, which is responsible for a common mechanism of pesticidal action (see below). Twenty-six such compounds have been identified (Appendix A) . It should be noted that the selection of compounds took place in January 2008. After this date, the EU evaluation of many of these compounds was finalised, resulting in either inclusion or non inclusion in Annex I, for reasons not necessarily related to the toxicological endpoints dealt with in this opinion. A number of triazoles share a common toxicological effect, either acutely or chronically. As a starting point, it was assumed that those compounds producing a similar effect might share a mode of action and therefore exhibit dose additivity (see below). Hence, in lower tier assessments they should be considered as members of the same CAG.

2.1.2. Similar mechanism of pesticidal action

The target site of all triazoles in fungi is the enzyme erg11/cyp51 (Appendix A). Fungicidal activity is a consequence of the direct inhibition of lanosterol-14-alpha-demethylase activity of CYP51, which is an essential step in ergosterol biosynthesis. Ergosterol is a derivative of cholesterol and is required for membrane fluidity and the integrity of fungal cell walls. Triazoles act by binding to the haeme iron in CYP51, thus inhibiting its activity which is detrimental to fungal growth (Zarn et al., 2003). The CYP51 gene is functionally conserved and is the only member of the CYP family having catalytically identical orthologues in plants, fungi, prokaryotes, and higher species. It encodes for lanosterol demethylase activity, critical for sterol biosynthesis in mammals.

In humans, the sterol 14-demethylase, i.e. CYP51, is expressed in many different tissues. It is therefore plausible that the mechanism by which the triazoles perform their fungicidal activity is the same as that responsible for some of the toxic effects in mammals, supporting consideration of these compounds in a CAG.

2.1.3. General mode/mechanism of mammalian toxicity

A number of adverse effects common to several triazoles has been observed in laboratory animals, such as developmental effects, effects on reproduction, hepatotoxicity, hepatocarcinogenicity in mice and the production of other types of tumours (thyroid, testis), via non-genotoxic mechanisms.

2.1.3.1. Developmental effects

To some extent triazoles show a typical pattern of developmental toxicity in laboratory animals. They are usually embryotoxic, cause delayed development (decreased foetal weight and/or delayed ossification) and also induce the following malformations and variations in rats:

Craniofacial or brain malformations (cleft palate, hypognathia, macroglossia, exophtalmus, hydrocephalus) observed with bitertanol, cyproconazole, diniconazole, epoxiconazole, flusilazole, propiconazole, triadimefon.

Variations of the urinary tract (dilated ureter and/or renal pelvis, absent renal papillae, hydronephrosis, and distension of urinary bladder) observed with cyproconazole, flusilazole, hexaconazole, propiconazole, tetraconazole, triadimefon and metconazole.

Additional cervical ribs observed with bromuconazole, diniconazole, epoxiconazole, flusilazole, myclobutanil, hexaconazole, penconazole, prothioconazole, tetraconazole, triadimenol and triticonazole.

See also Appendix B.

2.1.3.2. Reproductive effects

Reproductive toxicity, generally observed at parentally toxic doses includes impaired fertility, prolonged gestation, dystocia, reduced survival and reduced pup/litter weight, perinatal mortality. There is evidence for aromatase inhibition from in vitro and in vivo studies. Effects on reproduction are reported for bitertanol, cyproconazole, epoxiconazole, fenbuconazole, flusilazole, flutriafol, metconazole, myclobutanil, penconazole, prothioconazole, tetraconazole, triadimenfon, triadimenol and triticonazole.

See also Appendix B.

2.1.3.3. Hepatotoxicity, hepatocarcinogenicity in mice and other types of tumours (thyroid, testis)

Triazoles have been shown to have effects on the liver to various degrees (from enzyme induction, hypertrophy and increased liver weight to chronic inflammation and necrosis) and several of them induce mouse hepatocellular tumours and/or rat thyroid follicular cell tumours. There is evidence that tumour formation is via non-genotoxic mechanisms and that the tumours may be a consequence of effects on the liver.

For a detailed list of the hepatic effects of the substances see Appendix B.

2.1.4. Specific toxic effects

2.1.4.1. Developmental effects

Most of the developmental and teratogenic effects in rats occur at maternally toxic dose levels. In the rat, it was noted that malformations such as cleft palate and variations such as absent renal papillae were seen at high doses. While these were acknowledged to occur in the presence of maternal toxicity, they were considered to indicate a teratogenic potential not necessarily related to maternal toxicity. The finding of increased incidence of skeletal variations was considered to indicate some embryotoxicity, notably because the variations included extra cervical ribs which have a low spontaneous occurrence and may have serious developmental implications. The other skeletal variations seen were of less toxicological concern.

A number of triazoles cause specific cranio-facial malformations, which are potentially a consequence of acute exposure. Other developmental effects occurred with fewer compounds and/or were less specific.

2.1.4.2. Reproductive effects

In male rats, bitertanol administration resulted in increased relative testis weights, and in females, the absolute ovary and adrenal weights were decreased with histopathological changes (DAR).

Reproductive toxicity at parentally toxic doses of epoxiconazole included impaired fertility, prolonged gestation, dystocia, reduced number of viable pups, increased perinatal mortality, evidence for aromatase inhibition *in vitro* and *in vivo* (DAR).

Reproductive effects at maternally and paternally toxic doses of fenbuconazole, were dystocia, stillborns and litter loss (DAR).

Goetz et al. (2007) reported male reproductive effects in rats fed myclobutanil, propiconazole or triadimefon from gestation day 6 to postnatal day 120. Elevated serum testosterone levels, increased testis weights and ano-genital distance (AGD) and hepatomegaly, consistent with altered liver metabolism of steroids, were found at high dose levels of all three triazoles.

Rockett et al. (2006) studied the effect of myclobutanil, propiconazole and triadimefon on female rat reproductive development. It was concluded that developmental exposure to high dose levels of the triazole fungicides propiconazole, myclobutanil or triadimefon adversely impacted reproductive development in the female rat. AGD was increased by myclobutanil at high dose levels, vaginal opening was delayed by myclobutanil and triadimefon at high doses.

Taxvig et al. (2007) found that tebuconazole and epoxiconazole induced effects on reproductive development in the rat offspring after exposure in utero. The common features with the two tested fungicides were increased gestational length and the virilising effect on female pups.

2.1.4.3. Hepatotoxicity, hepatocarcinogenicity

In a 2-year rat study with flusilazole, compound-related microscopic lesions in the liver consisting of hepatocellular hypertrophy, cytoplasmic lamellar bodies, mixed foci of cellular alteration and fatty change were observed. Hepatocellular hypertrophy in males was predominately periportal with lamellar bodies, in females – mostly centrilobular with eosinophilic cytoplasm. Inhibition of liver P450 was found (DAR).

The liver was regarded as the main toxicological target organ in dogs and rats chronically exposed to bitertanol. Liver weight was found to be the most sensitive indicator. The activities of transaminases (AST and ALT), alkaline phosphatase, and glutamate dehydrogenase in the serum were increased. In addition, a rise in cholesterol level was observed in several studies in rats. The ability of bitertanol to induce hepatic mixed-function oxidases was verified in both species. It is likely that the effect on liver weight is due largely to hypertrophy of hepatocytes. Morphological changes in the liver were seen only at relatively high doses and consisted of hepatocytic swelling, bile-duct proliferation, perilobular fatty degeneration, eosinophilic foci, and fibrous structures (FAO/WHO, 1998).

Histopathological examination of propiconazole-treated rats identified the liver as the primary target organ, with increases in the incidence of enlarged liver cells. Liver effects included treatment-related macroscopic findings of enlarged livers and liver nodules/masses. Animals at the highest dose had a broad pattern of hepatic effects, including hepatocellular adenomas (FAO/WHO, 2004).

In a 2-year rat study with myclobutanil, the changes in the liver consisted of significant centrilobular to midzonal hepatocellular enlargement and vacuolization. The liver changes were consistent with increased liver-to-body-weight ratios in treated rats. The most sensitive end-point was testicular atrophy (DAR).

Triadimefon at concentrations of 25 mg/kg bw per day and above, reduced body-weight gains, increased liver weights and mildly increased liver enzyme activities. An increase in the ALT activity was found in males at high dose level and a decreased AST activity in all dosed females. In both sexes, a tendency to lower plasma bilirubin values at the intermediate and the highest doses and decreased creatinine values at the highest doses were observed (FAO/WHO, 2004).

In a 2-year rat study with triadimenol, the activities of liver enzymes in serum (ALT and AST and glutamate dehydrogenase) were increased (DAR, FAO/WHO, 2004).

Hepatocellular adenomas and adenomas/carcinomas have been observed in mice exposed to bromuconazole, cyproconazole, difenoconazole, diniconazole, epoxiconazole, fenbuconazole, fluquiconazole, flusilazole, metconazole, propiconazole, tebuconazole, tetraconazole, triadimefon and triadimenol.

2.1.4.4. Common metabolites

Three common metabolites have been identified: 1,2,4-triazole (free triazole), triazole alanine and triazole acetic acid. Triazole alanine and triazole acetic acid are formed in plants, and 1,2,4-triazole in both plants and animals.

Toxicological reference values for the triazole common metabolites have been set by several bodies, EPA (2006), EFSA (PRAPeR 14, 2007, not publicly available) and JMPR (FAO/WHO, 2008). However, there is no consensus on these values. The values may be used in risk assessment on a case-by-case basis, depending on the residue and toxicity profile of the parent compound.

For triazole alanine and triazole acetic acid, cranio-facial malformations were not observed (FAO/WHO, 2008). Therefore the PPR Panel concluded that there is no need to include triazole alanine and triazole acetic acid in the CAGs for acute effects. Chronic studies allowing a definitive statement for hepatotoxicity are not available for these 2 compounds.

Cranio-facial malformations were found with 1,2,4-triazole (FAO/WHO, 2008), albeit at doses higher than those of the parent compounds. No data are available on possible chronic effects of this compound. In addition, there is a lack of data on its occurrence in food commodities. It can be said only that the amount of 1,2,4-triazole found in rat urine varies from approximately 1% to 65% of the dose administered, depending on the parent compound. It was noted that there was no relationship between the occurrence of craniofacial malformations and the amount of 1,2,4-triazole found in rat urine. For the purposes of the current exercise, the PPR Panel decided not to include 1,2,4-triazole in the CAG for acute effects, although it should be noted that in a full assessment, the implications of this decision would need to be explored. In addition, the PPR Panel did not assess metabolites specific to individual triazole fungicides.

2.1.5. Conclusions

Amongst the effects of the triazoles, developmental toxicity is the only common acute effect produced by an appreciable number of the compounds. Hence, this endpoint was selected for the acute assessments in this case study.

While recognising that a first unrefined CAG could have included all compounds causing any developmental effect (i.e. cranio-facial malformation, variations of the urinary tract, additional cervical ribs), the PPR Panel decided to perform a refinement of grouping because data were available especially for cranio-facial malformation. In fact, variations of the urinary tract reflect an unspecific developmental delay, in most cases at dose levels higher than those causing cranio-facial malformations and involving some compounds, which also caused cranio-facial malformations. The additional cervical ribs are caused by an unknown mode of action, possibly reflecting some embryotoxicity. Another possible criterion for grouping could have been aromatase inhibition. However, the effect is not yet well documented and is unlikely to be maximal as a consequence of only a single dose.

On the basis of this information, the PPR Panel decided that for the purposes of this exercise it was most appropriate to perform a cumulative acute risk assessment using the seven compounds associated with craniofacial / brain malformations as the common effect. These are listed in Table 2. The craniofacial / brain malformations were the findings with the most convincing evidence for a specific effect with a common mechanism. The Panel noted that some of the other developmental effects might be due to a common MOA, possibly related to perturbation of enzymes of hormone synthesis. Hence, for a full regulatory assessment of combined exposures to triazoles it would be necessary to determine whether these effects could result in potential risks greater than those for the craniofacial effects.

It is also concluded that the liver is a common target for the triazoles, the common features being hepatic hypertrophy, resulting in increased liver weight, and changes in the activities of a number of P450 enzymes.

Whilst effects on the liver might be a consequence of short term exposure, the data available were for repeated exposure. For the purposes of this case study, effects on the liver were assumed to be a consequence of long term exposure. Hepatic effects occurred with a greater number of compounds at lower doses than reproductive effects (see Appendix B), and hence 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, and 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 (Table 2). For five of these, hepatotoxicity was the most sensitive end-point in rats and the respective ADIs were based on this effect (cyproconazole, diniconazole, epoxiconazole, propiconazole, difenoconazole). It should be noted that for a full regulatory assessment of combined exposures to triazoles, all of the compounds causing hepatotoxicity would need to be considered in the CAG, at least initially.

NOAELs for developmental, reproductive and hepatic toxicity of triazoles are presented in Appendix B.

2.2. Possible refinement of CAGs on basis of common toxic effects

2.2.1. Developmental effects

A number of compounds in the triazole group appear to have a common intrinsic teratogenic activity, the specific targets of which are the embryonic structures involved in cranio-facial and palate formation (Menegola et al., 2005). The suggested mechanism for the teratogenic effects involves the inhibition of embryonic CYP26 degradation of retinoic acid, as the effect is similar to that after exposure to exogenous all-trans-retinoic acid (Menegola et al., 2006). Triazole-related abnormalities are confined to structures controlled by retinoic acid, especially the neural crest cells, hind brain, cranial nerves, and craniofacial structures.

Although this common pathogenic pathway was demonstrated for four triazole-derivatives (the pharmaceutical fluconazole and the agrochemicals flusilazole, triadimefon and triadimenol), it does not appear to be due to the triazole moiety, per se. 1,2,4-Triazole itself induced only slight signs indicative of developmental retardation when tested in vitro at very high concentration levels (5000 μM) and the monotriazoles (used in agriculture) showed greater teratogenic potential than triazoles with bis-triazole rings (used as pharmaceuticals).

Seven triazoles – bitertanol, cyproconazole, diniconazole, epoxiconazole, flusilazole, propiconazole and triadimefon – have been shown to produce cranio-facial malformations. In view of this, and the findings of Menegola et al. (2005), it is concluded that these effects are most probably the consequence of a common mechanism of toxicity. On the basis of these considerations, all of the compounds in the acute CAG described in 2.1.3.1 were retained (Table 2).

2.2.2. Hepatic effects

The mechanism of hepatic toxicity of triazoles in mammals is still not very well characterised because multiple effects have been identified. Many triazoles act as ligands for nuclear receptors. Ligand-bound nuclear receptors heterodimerize with other nuclear receptors increasing the transcription of several CYPs including CYP2B and CYP3A members. In rodents one consequence of activation of nuclear receptors such as CAR is hepatic hyperplasia, and this might underlie some of the effects of the triazoles reported in the liver.

As discussed above, the fungicidal activity of triazoles is a consequence of their direct inhibition of CYP51 (lanosterol-14-alpha-demethylase). In mammals, CYP51 is part of the pathway leading to the biosynthesis of cholesterol which is the primary sterol in the cell membrane of mammals and is required for sex steroid hormone and vitamin D synthesis. Triazoles can also inhibit several other P450 enzymes, including members of the CYP1A, CYP2C and CYP3A sub-families, as well as CYPC19 and CYP26, though specificity varies with structure. Hence, the effects of triazoles on mixed function oxidase activity are a balance between induction and inhibition of a variety of CYP enzymes.

The USEPA and US Triazole Task Force have an ongoing collaboration with the aim of determining the mode(s)/mechanism(s) of action of conazoles (which comprise triazoles and imidazoles) by simultaneous traditional toxicology and transcriptional and metabolic profiling. Three conazole triazoles were selected as model compounds: myclobutanil, propiconazole and triadimefon. Wolf et al. (2006) showed that altered metabolism in the liver was a common response to all of these triazoles. It was not possible to identify a unique pattern of effects that could explain the toxic responses for these conazoles.

Four triazole fungicides, the pharmaceutical fluconazole and the agrochemicals myclobutanil, propiconazole and triadimefon were studied using toxicogenomic techniques to identify potential mechanisms of action. Adult male Sprague-Dawley rats were dosed for 14 days by gavage. Following exposure, serum was collected for hormone measurements, and liver (and testes) were collected for histology, enzyme biochemistry, and gene expression profiling. Body and testis weights were unaffected, but liver weights were significantly increased by all four triazoles, and hepatocytes exhibited centrilobular hypertrophy. The triazoles affected the expression of numerous CYP genes in rat liver (and testis), including multiple CYP2C and CYP3A forms as well as other xenobiotic metabolizing enzyme and transporter genes. Hierarchical clustering of CAR/PXR regulated genes demonstrated the similarities of toxicogenomic responses in liver between all four triazoles. The triazoles also affected the expression of multiple genes involved in steroid hormone metabolism (Tully et al., 2006; Goetz et al., 2007).

Toxicogenomic studies of myclobutanil, propiconazole and triadimefon in mouse liver suggest that triazoles have effects on the metabolism of retinoic acid (Ward et al., 2006; Chen et al., 2009). Hence, effects in the liver may play a role in the mode of action for the teratogenic effect of these compounds.

Although the mechanism of hepatic toxicity of triazoles has not yet been fully characterised and multiple effects have been observed, there is presently no evidence that these compounds would not act in a dose-additive way regarding hepatotoxicity. It was concluded that the CAG could not be refined and remained: bitertanol, cyproconazole, difenoconazole, diniconazole, epoxiconazole, flusilazole, myclobutanil, propiconazole, tebuconazole, triadimefon and triadimenol (Table 2).

Higher tier assessments may be possible when data on the mode/mechanism of action for the hepatotoxic effects of triazoles become available.

Table 2. List of triazoles selected for CAG

Triazoles for acute assessment	Triazoles for chronic assessment
bitertanol	bitertanol
cyproconazole	cyproconazole
diniconazole	difenoconazole
epoxiconazole	diniconazole
flusilazole	epoxiconazole
propiconazole	flusilazole
triadimefon	myclobutanil
-	propiconazole
-	tebuconazole
-	triadimefon
-	triadimenol

Structures of triazoles forming the CAG are given in Appendix B.

2.3. Hazard characterisation of compounds selected in CAGs for acute and chronic Cumulative Risk Assessment

Tables 3 and 4 summarise toxicological RVs and related RfPs for acute and chronic cumulative risk assessments. They have been extracted from DARs (Draft Assessment Reports) or JMPR evaluations that were available at January 2008. For this reason some of the figures may not be exactly the same as those adopted subsequently by EFSA in 'Conclusions' published in 2008 and 2009 for some of the compounds. Additional information can be found in Appendices B and C.

Table 3 RfPs and Reference Values (ARfD) for acute toxicity, adjusted Reference Values and RPFs for cranio-facial toxicity for triazoles included in the CAG for acute effects. Note that the data refer to status of evaluation in January 2008. For derivation of RPFs, see below.

	Critical effect		Common effect				
Compound	**NOAEL acute toxicity (mg/kg bw/d)**	**ARfD (mg/kg bw) UF**	**NOAEL (mg/kg bw/d)**	**Cranio-facial effect ARfD (mg/kg bw) UF**	**NOAEL-based RPF**	**BMD5 (mg/kg bw/d)**	**BMD5-based RPF**
Bitertanol	1.1	0.01 UF 100	30	0.3 UF 100	1.7	110	2.1
Cyproconazole	2	0.02 UF 100	12	0.12 UF 100	4.2	104	2.2
Diniconazole	5	0.02 UF = 25	80	0.8 UF 100	0.6	243	1.0
Epoxiconazole	2.6	0.026 UF 100	60	0.6 UF 100	0.8	154	1.5
Flusilazole	0.5	0.005 UF 100	50	0.5 UF 100	1	232	1.0
Propiconazole	30	0.3 UF 100	30	0.3 UF 100	1.7	2648#	0.1
Triadimefon	2	0.08 UF = 2	50	0.5 UF 100	1	198	1.2

The BMD5 for propiconazole is considered to be unreliable, see section 2.3.

The Critical Effect was the one upon which the ARfD was based. Note that this was not necessarily the common effect. The Cranio-facial effect ARfD is the value recalculated using the NOAEL for cranio-facial effects and a default uncertainty factor (100). The RPF was obtained from the ratio of the RfP (NOAEL or BMD5) for the common effect of the index compound (flusilazole) to that of the compound of interest.

Table 4 RfPs and Reference Values (ADI) for chronic toxicity, adjusted Reference Values, and RPFs for hepatotoxicity for triazoles included in the CAG for chronic effects. Note that the data refer to status of evaluation in January 2008. For derivation of RPFs, see below.

	Critical effect		Common effect		
Compound	**NOAEL chronic toxicity (mg/kg bw/d)**	**ADI (mg/kg bw/d) UF**	**NOAEL (mg/kg bw/d)**	**Hepatotoxic effect ADI (mg/kg bw/d) UF**	**NOAEL - based RPF**
Bitertanol	0.1	0.001 UF 100	1	0.01 UF 100	2.0
Cyproconazole	2	0.02 UF 100	2	0.02 UF 100	1.0
Difenoconazole	1	0.01 UF 100	1	0.01 UF 100	2.0
Diniconazole	5	0.02 UF 250	5	0.05 UF 100	0.4
Epoxiconazole	0.8	0.0032 UF 250	0.8	0.008 UF 100	2.5
Flusilazole	0.2	0.002 UF 100	5*	0.005 SF 1000	4.0
Propiconazole	3.6	0.04 UF 100	3.6	0.036 UF 100	0.6
Myclobutanil	2.5	0.025 UF 100	39	0.39 UF 100	0.05
Tebuconazole	3	0.03 UF 100	16	0.16 UF 100	0.1
Triadimefon	3.4	0.03 UF 100	16.4	0.16 UF 100	0.1
Triadimenol	4	0.01 UF 300	5	0.05 UF 100	0.4

*LOAEL

The Critical Effect was the one upon which the ADI was based. Note that this was not necessarily the common effect. The Hepatotoxic Effect ADI is the value recalculated using the NOAEL for hepatotoxicity and a default uncertainty factor (100). For flusilazole, a SF of 1000 was used as the RfP was a LOAEL(Lowest Observed Adverse Effect Level). The NOAEL for this compound was set at 0.5 mg/kg bw/d. The RPF was obtained from the ratio of the NOAEL for the common effect of the index compound (cyproconazole) to that of the compound of interest.

2.4. Selection of Index compounds

The RPF method requires the identification of an IC. The potencies of all chemicals in the CAG are normalized to the IC.

The IC selected in the CAG for acute assessment was fluzilazole based on the most complete toxicity data for the common end-point. The ARfD is based on the developmental effect, which has been well characterised for flusilazole.

The IC selected in the CAG for chronic assessment was cyproconazole as the ADI is based on liver effects and the DAR contained a comprehensive database.

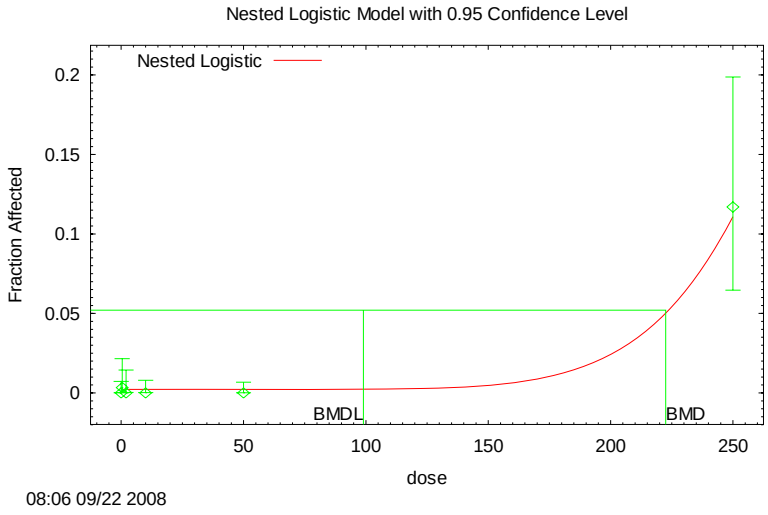
2.4.1. Calculation of acute RPFs

RPFs based on flusilazole and using the NOAEL approach are given in Table 3.

For acute assessment the relative potency was also calculated based on BMD 5 (Table 3).

The BMD evaluation was performed using the BMDS software (version 1.4.1c) from the US EPA[5]. A nested logistic model was run using data on the number of affected pups in individual litters. This method required many details for the modelling, which were not available in most DARs and the information had to be retrieved from the original reports of the developmental studies. Default settings, other than the 'effect level', were not altered. Initial runs used a range of response levels (10% to 0.5%). The PPR panel decided to use a 5% response level because it is generally at or near the limit of observable response for developmental effects – 1 affected litter out of a group size of 20. This is in accordance with the recommendations given in the opinion of the EFSA Scientific Committee on the BMD approach (EFSA, 2009). The dose response curves for many of the compounds were not ideally suited to determination of a BMD, with a clear response only at the top dose level. This was particularly true for propiconazole, for which the inbuilt statistical analysis package identified that the BMD results were subject to a high level of uncertainty.

Figure 5. Example of the BMD plot for the index compound, flusilazole



[5] http://www.epa.gov/NCEA/bmds/index.html

2.4.2. Calculation of chronic RPFs

RPFs for chronic effects were based only on NOAELs. A BMD approach was not used for the chronic assessment. This decision was based on several factors:

- The NOAELs reported for hepatotoxicity were based on a variety of end-points in the different studies e.g. changes in enzyme level (increased ALT and AST activity), increased liver weights, hepatocellular hypertrophy, occurrence of cytoplasmic lamellar bodies, mixed foci of cellular alteration and fatty change, significant centrilobular to midzonal hepatocellular enlargement and vacuolization.

- In some cases, species other than rats (mice, dogs) were used for selection of the lowest NOAEL for hepatotoxicity.

To resolve these points would require significant re-evaluation of the individual study reports to determine an appropriate common end-point in one species. Once this had been determined, the data for the BMD input would have to be extracted from either summaries or individual study reports. It was considered that the amount of work involved in deriving BMDs was likely to be disproportionate to the impact on the final outcome of the exercise .

2.4.3. RPFs based on NOAELs versus BMDs.

The PPR Panel noted that propiconazole had an RPF of 1.7 based on NOAELs and 0.1 based on a BMD5. Potential reasons for this discrepancy were investigated. The number of foetuses with craniofacial lesions following propiconazole exposure (n=2; equivalent to ca 1%) was the lowest of all the compounds in the CAG, and the top dose level of 300 mg/kg bw/day was equal highest (see Table 5). This gives a shallow dose response which produces a relatively high BMD5, with a high level of uncertainty, i.e. there was a large difference between the BMD and the BMDL and a low RPF. For comparison the reference compound, flusilazole had a much higher incidence of 49 affected foetuses at the lower top dose level of 250 mg/kg bw/day. Conversely, because the background incidence of craniofacial lesions in rats is typically zero, the one affected foetus from the 90 mg/kg bw/day propiconazole group drives the NOAEL down to 30 mg/kg bw/day whereas the NOAEL for flusilazole is 50 mg/kg bw/day[6]. The differences in RPFs are therefore attributable to the differences in approach, the BMD being based on the dose giving a predefined magnitude of response and the NOAEL being based on the highest tested dose giving zero response.

On the other hand, the Panel noted that, where it was possible to determine reliable BMD values (all compounds except propiconazole), the RPF values derived from NOAELs and BMD5s were comparable (see Table 3).

[6] Although the response at these doses was not statistically different from that in the control, it was considered to be of potential biological significance.

Table 5. Craniofacial findings for compounds in the acute CAG

	Foetuses affected*	Litters affected*	Dose levels affected
Flusilazole	49	15	250 mg/kg bw/d
Bitertanol	4	3	100 mg/kg bw/d
Cyproconazole	10	2	120 mg/kg bw/d
Diniconazole	140	17	300 mg/kg bw/d
Epoxiconazole	137	18	20 (n=1) & 180 mg/kg bw/d (but none at 60mg)
Propiconazole	3	3	90 (1) & 300 (2) mg/kg bw/d
Triadimefon	7	4	75 (2) & 100 (5) mg/kg bw/d

* the values shown are the sum of the responses for the dose levels in the final column. In the final column, the values between brackets are the number of foetuses affected.

3. Cumulative exposure assessment of triazoles

3.1. General issues on exposure calculations

For this opinion, the deterministic exposure estimations for triazoles were made by the PPR Panel itself by using the EFSA PRIMo model for chronic and acute risk assessment (rev. 2.0)[7] (EFSA, 2007a; pages 22 – 26, Table 2.2.2-1 and 2.2.2-2), whereas the probabilistic calculations (tier 4) were commissioned to the Rikilt Institute of Food Safety (contract NP/EFSA/PPR/2007/01, Title: "Cumulative Exposure Assessment of triazole fungicides ").

The EFSA model was designed by the EFSA PRAPeR Unit to be used for the risk assessment of proposed temporary MRLs according to Regulation 396/2005 (EFSA, 2007a). It calculates dietary exposure per compound, by use of the internationally recognized IESTI, TMDI and IEDI equations (WHO, 1997a), which have been used and described by the PPR Panel in other opinions. The cumulative exposure to a group of pesticides, like the triazoles, can be calculated by rerunning the model for each compound in the CAG and summing up the contributions from each of the individual pesticides in the group after adjusting for their relative potencies.

The reader is referred to Chapter 1.3 for the rationale for choosing either the level of the MRL, the STMR or monitoring data as the relevant concentration data in the calculations in each of the scenarios. The choice of consumption data for the 'total population' versus 'eaters only/consumers only' is explained there as well.

For the current worked example, Rikilt Institute had an electronic platform that was created within the EU-project SAFE FOODS (www.safefoods.nl) (QLRT number Food-CT-2004-506446). Within this project, food consumption and pesticide residue data from five European countries were made compatible with each other. Residue and food consumption data of the different countries were connected via the Internet with the Monte Carlo Risk Assessment (MCRA) software, which can be used in a user-friendly way via the web[8]. Drawing on this experience for the current project, food consumption and

7 In context of evaluation of temporary MRLs, EFSA created a European food consumption database by collecting all the consumption data already available at Member State level (national diets) and at international level (i.e. the GEMS/Food WHO diets). It was named EFSA PRAPeR database (EFSA, 2007a) after the name of the unit within EFSA who set-up this database (PRAPeR: Pesticide Risk Assessment and Peer Review). Version 2 of the EFSA model has been renamed EFSA PRIMo (Pesticide Residue Intake Model) database (EFSA, 2008b and 2008c). The PRIMo database was used in this opinion for the deterministic exposure calculation.

8 See https://mcra.rikilt.wur.nl/

residue databases were used from Czech Republic, France, Italy, The Netherlands, Sweden, United Kingdom and Finland (the last only for residue data).

The probabilistic exposure estimations are described and discussed in detail in the report from the Rikilt Institute (van Klaveren et al., 2009). A probabilistic MCRA model was used to estimate the distribution of one-day intakes. For long-term intake assessments, three statistical models were tested to minimise the within-person variation. The exposure assessments were performed for 5 different Member States, with different age groups and for different scenarios. The goal of half of the scenarios was to calculate the actual exposure using monitoring data only. In the other half of the scenarios, Maximum Residue Limits (MRLs), STMRs or field trial data for the particular agricultural commodity of interest were used as input for calculating the possible exposure levels as a consequence of MRL setting. In this type of calculation, monitoring data for all other food or RAC (Raw Agricultural Commodity) -pesticide combinations were used as input to account for the background level of cumulative exposure. The estimations were carried out both at national level for each of the individual Member States and at European level by pooling of all the monitoring data and performing the calculations using the six different consumption databases addressing the variation in consumption patterns in different parts of Europe.

Basically, the probabilistic estimations of the cumulative dietary exposure are made by the use of RPF-factors to combine separate exposure distributions for the different triazoles into one probability distribution for the cumulative exposure. The main challenge is how to deal with samples in which not all triazoles are analyzed. Two approaches were considered. The first approach starts with summing the concentrations of different triazoles in the same sample according to their corresponding RPF. This accounts for correlations in the use pattern of pesticides. Because in practice not all samples are analyzed for all triazoles, it is difficult or impossible to accurately estimate the 'possible' concentration values of the non analyzed triazoles in each sample. Approach 1 considers these triazoles as non-detects (or zero values if it is assumed that a non-detect is a zero). This might lead to an underestimation of the exposure because in reality those non-analyzed triazoles might have actually been present. Therefore a more pragmatic alternative approach was pursued, which simulates all samples of each triazole separately and finally sums the results of the separate simulations according to the corresponding RPF in a later stage of the cumulative exposure calculations. In this pragmatic approach, the calculation was limited to the number of analyzed values for each triazole and no assumptions were made for non-analyzed triazoles. Because the first approach could underestimate the exposure, the second approach was used in all the calculations, with the exception of the uncertainty analyses as described in Chapter 5. As for the deterministic calculations, the same four different scenarios were addressed for the probabilistic estimations, i.e. acute and chronic exposure at actual exposure level (monitoring level) and for MRL-settings.

The PPR Panel performed the deterministic calculations (tiers 1-3) using French and Dutch consumption and residue data (as representatives for Southern and Northern Europe). Since the Dutch data were the most comprehensive, and the results for France and The Netherlands did not differ to a great extent, it was decided to report the results with the Dutch data in the opinion itself, and the French results in the Appendix. Residue data were identical to the data used by Rikilt Institute. However, consumption data were used as present in the EFSA PRIMo model (Large Portions (LP), representing the 97.5 percentile of consumption of the RAC, and mean consumption of the RAC), whereas Rikilt Institute had access to the raw food consumption data itself, including consumption of processed foods. In the PRIMo, the raw data had already been converted to Large Portions and mean consumptions. The calculations were performed for the general population of these countries, plus for children.

It should be noted that the work done by the PPR Panel and the Rikilt Institute was done in parallel. Some discrepancies between the deterministic and probabilistic tiers are noted, either caused by the timing of the work, or by the different nature of the two approaches. Discrepancies can be found in the handling of Non-Detects (NDs), the extrapolations and processing factors used, assumptions regarding processed foods and RACs, variability factors and, in the case of the MRL setting scenario, in the residue data used (national data in deterministic and national or pooled data in probabilistic assessment). This will be considered when comparing the outcome of the deterministic and probabilistic tiers (Chapter 4 and 6).

3.2. Residue data for the triazole exercise

3.2.1. Residue definitions for compounds in the CAG

For cumulative risk assessments, parent compounds, metabolites and degradation products are of concern only when they have the same common effect/mode of action being considered within the CAG. This should be assessed for each CRA. The triazole common metabolites, 1,2,4-triazole, triazole-alanine, and triazole acetic acid and other metabolites specific to individual triazole compounds were not included in the worked example, see 2.1.4.4 for rationale.

The current residue definitions for monitoring residues of nine of the active substances in the CAG bitertanol, cyproconazole, difenoconazole, diniconazole, epoxiconazole, flusilazole, myclobutanil, propiconazole, and tebuconazole are parent only. Triadimenol and triadimefon are different in that a common MRL definition exists for these two similar compounds which is the sum of triadimefon and triadimenol.

3.2.2. Supervised trial data

Within the Rikilt Institute project, supervised trial data were sought from JMPR reports and Draft Assessment Reports produced for Annex I inclusion evaluations, under Directive 91/414/EEC. The available field trial data, associated STMRs and the current MRLs[9] used for the selected pesticide/commodity combinations in the MRL-setting scenarios are shown in Appendix D.

In both the supervised trials and monitoring situations discussed below measurements were made in composite samples of the RAC.

For this worked example no assessment was made of the potential for residues of parent to occur in rotational crops or of the potential for residues to occur in animal products. However, examination of the DARs for the individual compounds indicates that both these events are unlikely.

3.2.3. Monitoring data

Residues data from several European countries including the Czech Republic, Finland, France, Italy, The Netherlands, Sweden and the United Kingdom were used in the worked example. The number of triazole pesticides analysed varied between countries and with RAC. An overview of the data is provided in Appendix E (for more details see van Klaveren et al., 2009, Annex 1).

Some of the data from each Member State were collected as part of the EU coordinated programme, and these samples will have been collected on a non-targeted basis. However, the degree to which the individual complementary official monitoring programmes follow random sampling procedures, or incorporate targeted sampling, is not generally transparent. In general, the analytical aspects of the programmes comply with appropriate quality assurance systems, however this was not explicitly reported in all cases.

The monitoring data contributed to the deterministic assessments by providing information on the "background" levels of intake (see Section 3.4). Furthermore, they are the residue of choice when an 'actual exposure' assessment is performed.

In many countries different analytical methods were used within the same lab. In addition several laboratories could have performed the pesticide analysis using different analytical methods. It was considered to be impossible within the timeframe and resource available in this exercise to ask detailed questions regarding the analytical method and limits of detection (LOD) or quantification (LOQ) for each separate analytical result reported by Member States involved in this exercise. To avoid misinterpreta-

[9] See EU Pesticides Database for EU-MRLs: http://ec.europa.eu/sanco_pesticides/public/index.cfm

tion between LOD and LOQ, and for practical reasons, Member States were asked to comment and to quantify the limit of reporting (LOR) in a more generic way. A few Member States reported that the LOR varied per food item, per pesticide, per analytical method used to analyse the pesticide in a particular food item, per laboratory and per year of sampling. In 2007 for example more accurate methods might have been used compared to 2003 (for more details see van Klaveren et al., 2009). It should be noted that the LOR value greatly influences the number of NDs reported (see section 3.2.7).

It was also observed that in many countries not all samples were analysed for an equal number of triazoles. In the Czech Republic for example 211 samples of apples were analysed for triademefon. Out of these 211 samples 114 were also analysed for bitertanol and only 24 for myclobutanil. An unequal number of triazoles analysed per sample hampered an overview of co-occurrence of pesticides within the same sample. It also hampered the use of some of the models as reported by van Klaveren et al. (2009).

3.2.4. Extrapolation of residues data

While not all pesticides belonging to the CAG were analyzed in all possible RACs in the monitoring data, extrapolation of measured residue concentrations from measured RAC to similar RACs using relationships shown in Appendix F was considered. Such extrapolation was performed for the probabilistic assessments only. For example, tebuconazole levels in pear were extrapolated to levels in apple if tebuconazole was not analysed in apple.

Extrapolation was considered separately for each country's monitoring data and the combined pooled data. It was only considered where there were no monitoring data for the residue commodity combination and where the relevant MRLs were set above the LOQ. In addition, extrapolations were only made using the appropriate EU guidance documents (EC, 2008) where the MRL of the measured residue and the MRL for the unmonitored residues in the commodity were the same or very similar. Annex 3 of the RIKLIT Report provides details of the combinations where extrapolations were made.

3.2.5. Processing data

As stated above, the residue concentrations in both the supervised trials data and the monitoring data were measured in the RAC. Although some commodities might be consumed after no or very little processing, others might be subject to various degrees of processing, while some are always subject to some form of processing such as peeling.

The consumption data in PRIMo used in the deterministic estimates typically represent the sum of all the forms of food through which the commodity is consumed after back calculation to the RAC, or data on the RAC as such[10]. For example, consumption of fresh apples would sometimes be combined with consumption of apples that were juiced, and sometimes not. However, either way no information on LPs of processed foods is available. Consequently, without consumption data specific to the different processed commodities it was not possible to apply processing factors to these estimates as processing factors are different for the different food forms.

[10] This issue may have been handled differently by different MS when supplying data on 97.5 percentiles of consumption (eaters only) to EFSA to build the PRIMo. In the Netherlands, at first all processed foods were calculated back to RAC. However, it was considered that the 97.5 percentile of a particular food was much lower than would be expected when all processed foods were calculated back to RAC and included in the distribition. At that time it was explained by the dilution of the 'eaters only' population caused by food items having the RAC as a minor ingredient (e.g. apples or tomatoes can be found in 50 different food items). Including many consumers in the calculation that ate only minor amounts of the commodity (in processed form), extended the distribution in the lower area and consequently, the 97.5 percentile shifted downwards. Since for the acute intake, the interest is mainly in the crop unit with the high residue, and not with small amounts of processed crop containing only small amounts of residue, it was decided to calculate the 97.5 percentile of consumption of the RAC eaten as such. This is in accordance with the recommendation by WHO (WHO, 2008).

The probabilistic models do keep the consumption of different food forms separate and, where relevant, residue concentrations in RACs were adjusted using fixed processing factors to reflect the different concentration expected in the consumption data food forms. Data on the effects of processing on the residues in the CAG were sought from JMPR evaluations, Draft Assessment Reports done under Directive 91/414/EEC and UK pesticide evaluations. Details of specific processing factors for different pesticide commodity combinations are in Appendix G.

3.2.6. Handling of variability factor

In the deterministic approach to calculate cumulative acute exposure, variability factors were applied with values depending on the unit weight of the crop as defined in PRIMo, using the highest value when more than one option was available.

In the probabilistic approach, a fixed value of 3.6 was used as variability factor, the so called stochastic variability factor for market samples of food commodities, as described in the EFSA opinion on the appropriate variability factor and applied in the opinion on acute dietary intake (EFSA 2005, 2007b).

A variability factor was not applied to either of the chronic intake calculations, neither deterministic nor probabilistic.

3.2.7. Handling of non-detects

It is well known from risk assessments of dietary exposure to individual pesticides that the methods for handling NDs can have a great impact on the extent of the estimated exposure. This is indeed also the case when assessing cumulative intake, especially when using deterministic methods. The use of censored data was broadly described and discussed by the PPR Panel in their recent opinion on existing methodologies to assess cumulative risks from pesticides (EFSA, 2008a). It was emphasized by the Panel that the use of censored (truncated) data is a significant issue, which should be considered carefully, and the Panel proposed that a sensitivity analysis be performed in order to assess the uncertainty of the estimations.

The handling of chemical contaminant data reported to be below quantifiable limits is a general concern in most of the exposure assessments carried out by EFSA. The Datex Unit of EFSA has recently established a working group with the objective of proposing standardised guidance to handle left censored distributions of data. This task is currently in progress.

There are currently a number of available methods for incorporating ND samples into a quantitative exposure assessment of pesticides. ND samples could be treated as being zero (containing no residue at all), treated as containing the full LOQ (or LOR in case of monitoring data), or treated as containing a concentration somewhere between these two extremes. In reality, it is known that some (unknown) fraction of the ND samples truly contain no residues (i.e., a zero concentration) because these samples were not treated. However, it is not known what fraction of the ND samples represent true zeros and what fraction represents residues < LOQ (or LOR in case of monitoring data), but greater than zero. One way to handle this is to assume that the fraction of NDs which represent a true zero is similar to the percentage of crops not treated. This is standard practice in the USA for single chemical assessments and is done as a sensitivity analysis for cumulative assessments (EPA, 2000) but is not commonly performed in Europe. In fact, in Europe such statistics are available only to a limited extent. In addition, the high turnover of imported and exported foodstuffs makes it very difficult to attach any percentage of the crops (un)treated to monitoring data. Even at local regional scales, very large differences can occur. Nevertheless, scenario analyses (assuming e.g. 25%, 50% and 75% crops treated) can help to illustrate the importance of this variable and the effect on the exposure assessment. NDs that contain the pesticide can be assigned any level equal to or below LOQ (or LOR in case of monitoring data), either as a point estimate (all NDs at the same level) or a distribution. A variety of analyses could be performed to evaluate the sensitivity of the exposure estimates at a given percentile to any assumptions regarding the concentrations associated with ND values and what proportion of the crop is treated.

There is no specific information on the use pattern of the individual triazoles for the Dutch and French monitoring data, which were available for the deterministic intake estimations. Thus the percentage of crops that has been treated is unknown. Furthermore, it is not known if all commodities have been treated with all the triazoles, or if crops, which are not included in the monitoring programmes, have been treated and therefore could be another source for exposure. Considering these uncertainties it was decided to perform the deterministic calculations of the background exposures to triazoles under the assumption that residue levels in samples with residues below LOR are at ½LOR for commodities with any detectable residues but at 0 for commodities without any detected residues (see Section 3.4). The same assumption was made for the deterministic exposure estimations of all four scenarios. In contrast to this, the probabilistic estimations were made under the assumption that residues below the LOR are 0. As a consequence, the deterministic estimated exposures (whether acute or chronic) are expected to be higher than the corresponding probabilistic estimations. The significance and sensitivity of this assumption are further discussed in Chapter 5 on sensitivity/uncertainty.

3.3. Consumption data for the triazole exercise

3.3.1. Consumption data used for tier 1 to tier 3 - deterministic modelling

The requirements on consumption data for the use in cumulative dietary exposure have been described by the PPR Panel (EFSA, 2008a). For the worked triazole example, version 2 of the EFSA PRIMo model (EFSA, 2008b and 2008c) was used for the deterministic exposure calculations. The EFSA model is based on the EFSA food consumption database, which includes national food consumption data from several Member States. At present, the model includes consumption data for adult consumers from 12 Member States and data for children from 7 Member States. Furthermore, the model includes data from the WHO European Regional diet[11] and the 4 WHO cluster diets B, D, E and F (WHO, 2006). Consumption data from France and the Netherlands (countries which were chosen to focus on in the worked example) are included for both adult consumers and for children.

In this worked example, the Panel decided to calculate the cumulative dietary exposures using deterministic modelling based on consumption data of the Netherlands and of France, selected from the EFSA PRIMo model. The reasons for this selection were:

- The fact that consumption data for the Netherlands and France in the PRIMo database (mean consumption and Large Portions –the latter for the Netherlands only-) were derived from the same food consumption surveys for which the total distribution is available in the SAFE FOODS database used in tier 4,
- The aim to cover the Northern and Southern European regions, one country each should be included in the example,
- The availability to Rikilt Institute to be used in the MCRA platform.

The PPR Panel decided to use the Dutch data as an example for Northern Europe and the French data as an example for Southern Europe. However, as indicated in 3.1, since the Dutch data were the most comprehensive, and the results for France and The Netherlands did not differ to a great extent, it was decided to report the results with the Dutch data in the opinion itself, and the French results in appendixes I and J.

The Netherlands provided EFSA with national chronic (mean) and acute (97.5th percentile) dietary intake data for both children and the general population (Anonymous, 1998). The survey was carried out in 1997/98 for 2 consecutive days of a diary record. The number of respondents was 6250 for the gen-

[11] It should be noted that WHO has replaced the regional diets by the cluster diets, since they are based on more recent food balance sheet data

eral population in the age range 1 – 97 years with a mean body weight of 63 kg. For children, the number of respondents was 530 in the age range of 1 – 6 years with a mean body weight of 17.1 kg.

France provided consumption figures for the chronic exposure estimates only. The French model includes one consumption dataset for adults and two sets of data for children (Fr-infants and Fr-toddlers). Figures were derived as mean values from the "all population" (Nichele et al., 2005; Boggio, 1999). The survey was carried out in 1997 as a record of food purchases. The number of respondents depended on the commodity and ranged from 6110 to 16246 individuals with a mean body weight of 60 kg. For French children, the survey was carried out on 3 consecutive days as a diary record. The number of respondents was 198 for infants in the age range of 7 – 12 months with a mean body weight of 8.8 kg. For toddlers, the number of respondents was 78 in the age range of 13 – 18 months with a mean body weight of 10.6 kg.

3.3.2. Consumption data used for tier 4 – probabilistic modelling

Probabilistic modelling was used by van Klaveren et al. (2009) to perform cumulative exposure assessments. The acute and chronic cumulative exposure calculations were done using different food consumption data from several countries which were collected within the EU Project SAFE FOODS (www.safefoods.nl; QLRT number Food-CT-2004-506446). Food consumption data from the different countries are connected via the internet to the Monte Carlo Risk Assessment (MCRA) software (de Boer and van der Voet, 2007). In this way, an electronic platform was created which can be used in performing exposure assessment in a standardised way addressing the exposure to pesticides in different European countries. The input for the probabilistic software consisted of food consumption data from Czech Republic, France, Italy, The Netherlands, Sweden and United Kingdom. The food consumption database included the raw consumption data. Food as eaten was converted back to its corresponding RACs in order to make food exposure expressed on an "as eaten" basis compatible with the agricultural commodities which were analyzed for triazoles. An overview on consumption data used in the probabilistic exposure assessment by Van Klaveren et al. (2009) is shown in Appendix H.

RACs are more or less similar in different countries, making harmonisation at that level feasible. In order to be able to combine all the national residue data to the different national food consumption databases, the food coding of the national food consumption databases was also harmonised at RAC level. Within the SAFE FOODS project, food consumption data from Denmark, Sweden, the Czech Republic and Italy were linked to what were judged as similar foods coded in the Dutch food consumption survey. The food coded in the British Food Consumption Survey was converted in a similar way to RACs.

In the cumulative exposure assessment, both foods consumed directly in raw form (e.g. apple, lettuce) and those present in processed (or multicomponent) dishes (e.g. pizza, apple juice) must be considered. In order to appropriately consider and incorporate both raw and processed foods in the assessment, all foods need to be converted to and expressed on a RAC basis; to do this, food conversion tables or databases should be available so that the ingredients in multi-component foods can be incorporated. In both the Dutch and French databases, this conversion model is present and multi-component foods are 'disaggregated' to their component parts expressed in RAC form. However, due to lack of food conversion models in the other European Member States, the Dutch food conversion table was used, thereby implicitly assuming that similar foods in Europe consist of the same RAC ingredients in equal weight percentages. For the description of the Dutch food conversion model, see van Dooren et al. (1995).

To estimate acute exposure to single chemicals, the model MCRA uses Monte Carlo simulation in which individual food consumption records are re-sampled from food consumption databases and combined with concentration distributions (empirical or fitted distributions). Sampled food consumption amounts of different foods and food forms (e.g. apple peeled, apple juice, apple sauce) are portioned into standard-sized units (each of size "portion size") using a list of unit weights; residue concentrations are modified by processing and variability factors to incorporate processing and unit-to-unit variability, respectively. For example, the unit weight of apples is 112 grams, and an individual who reported consuming 250 grams of apples would be recorded as having consumed 3 "portions" of apples, two of

"portion size" 112 grams and one of "portion size" 26 grams. It may be noted that for chronic exposure the division of the consumed amounts into separate portions is unnecessary. The exposures are calculated for multiple days per individual. A typical food consumption survey includes 2-7 days of reporting (or recalling) food consumption. The Rikilt Institute has used different statistical models to address the long-term intake (de Boer and der Voet, 2007; de Boer et al., submitted; Dodd, 1996; Nusser et al., 1996 and 1997; Slob, 2007). These models were based on the variation of consumption within individuals (different days of the same individual reported in the food consumption database) and variation of intakes between individual consumers. This modelling approach enables the risk assessor to estimate the whole distribution of life-long exposure levels of all individuals and also exposure levels of individuals with above average fruit and vegetable consumption.

3.4. Calculation of background exposures

For the deterministic exposure tiers (all scenarios), it is necessary to define the so-called 'background exposure'. For both acute and chronic exposure assessments, the PPR Panel defined this background exposure as the summed chronic exposure from all pesticides included in the respective CAG, based on national monitoring residue levels. In the probabilistic tiers, this background is automatically included by the method employed.

Thus, the background exposures include the actual exposures at monitoring level from the 7 triazoles in the acute CAG in all commodities when assessing acute cumulative exposure and the actual exposures at monitoring level from the 11 triazoles in the chronic CAG in all commodities when assessing chronic cumulative exposure.

Similarly to the approach taken by US-EPA for treated crops with non detect residues[12] (WHO 2008a), the deterministic calculations of the background exposures were made assuming that the residue levels in samples where the measured concentration was below LOR were equal to ½LOR for commodities where in at least one sample detectable residues were found, because this showed that the crop had been treated. Where all measured levels were below LOR, the Panel assumed that the crop had not been treated and a zero was assigned as residue level in the non-detect samples of these commodities. A sensitivity analysis was performed to evaluate and assess the impact of this assumption (see Chapter 5).

Although triadimenol is included in the MRL residue definition of triadimefon, the two residues are measured separately so that it is possible to include their specific contribution to the background exposures in a separately.

Background exposures have been calculated for Dutch and French consumer groups separately (see Appendix I). In a few cases the monitoring data include residues detected in commodities, for which there are no consumption data available for Dutch and or French consumers (for instance "parsley"). In those cases the calculations are based on WHO consumption data, primarily the WHO cluster diet E for the western part of Europe, if these data were available, otherwise the WHO regional diet for Europe was used. This is considered as a conservative estimation of the exposure since the WHO consumption data are based on trade data.

The combined background exposure was calculated as the potency-adjusted (using RPFs) sum of average chronic exposures to each of the triazole pesticides in the CAG. The individual contribution of each pesticide was first determined as the sum of the products of the average residue levels in food commodities and the average daily consumption of the commodities:

Exposure to a single pesticide *j*:

[12] US-EPA uses PercentCropTreated information to determine that fraction of the samples which have zero residues. The remainder of the samples that have ND residues are assigned ½ LOQ. Of course, the samples that have measureable residues are left as they are. So US-EPA has three "sets" of data for any given crop: (i) the treated detects with measured residues; (ii) the treated ND which are assigned ½ LOQ; and (iii) the non-treated NDs which are assigned a residue of zero.

$$E_j = \sum_{i=1}^{n_i} \left(I_i * C_{i,j} \right)$$

I_i = Average daily intake of commodity *i*

$C_{i,j}$ = Average residue level of pesticide *j* in commodity *i*

n_i = Total number of commodities

After transformation of the individual exposures into equivalents of the IC (using both NOAEL and BMD5 derived RPFs regarding cranio-facial toxicity for the acute CAG and using only NOAEL derived RPFs regarding hepatotoxicity for the chronic CAG), the cumulative exposure is found by summing the contributions from each individual pesticide in the CAG:

Cumulative background exposure:

$$\sum_{j=1}^{n_j} E_j = \sum_{j=1}^{n_j} \left(RPF_j * \sum_{i=1}^{n_i} \left(I_i * C_{i,j} \right) \right) = \sum_{j=1}^{n_j} \left(RPF_j * E_j \right)$$

RPF_j = Relative Potency Factor for pesticide *j*

The combined background exposure to triazoles included in the CAGs for acute and chronic effects is summarised in Tables 6 to 9.

Calculation methodology: EFSA PRIMo model

Consumption data: Dutch average long-term consumption of the general (1-97 years) and children (1-6 years) from a 1997-8 dietary survey (Anonymous, 1998).

Residue data: Dutch monitoring data from 2002-2007. For each pesticide/commodity combination, the arithmetic mean was determined. NDs values were allocated a level equal to ½ of the LOR for pesticide/commodities combinations with at least one positive finding in Dutch national monitoring results. For all other combinations ND values were considered as 0. The residue levels in unmonitored commodities were considered as 0 (no extrapolation applied).

Edible portion factor and processing factors: not applied because PRIMo contains only very limited consumption data on processed foods. Therefore it was not possible to combine a residue in processed food (derived from the residue in the RAC times the processing factor) with the appropriate consumption value. Consequently, it was considered that all commodities were consumed entirely as raw commodities.

Table 6. Combined background exposure of triazoles causing acute effects (cranio-facial toxicity) for the Dutch general population

Compound	Average chronic exposure				
	µg compound/kg bw/d	RPF (from NOAEL) for acute effect	µg flusilazole eq./kg bw/d (NOAEL)	RPF (from BMD5) for acute effect	µg flusilazole eq./kg bw/d (BMD5)
Bitertanol	0.037	1.7	0.063	2.1	0.078
Cyproconazole	0.037	4.2	0.157	2.2	0.082
Diniconazole	0.031	0.6	0.019	1	0.031
Epoxiconazole	0.024	0.8	0.019	1.5	0.036
Flusilazole (IC)	0.038	1	0.038	1	0.038
Propiconazole	0.037	1.7	0.063	0.1	0.004
Triadimefon	0.070	1	0.070	1.2	0.085
Combined background exposure	-	-	**0.429**	-	**0.354**

Table 7: Combined background exposure of triazoles causing acute effects (cranio-facial toxicity) for Dutch children

Compound	Average chronic exposure				
	µg compound/kg bw/d	RPF (from NOAEL) for acute effect	µg flusilazole eq./kg bw/d (NOAEL)	RPF (from BMD5) for acute effect	µg flusilazole eq./kg bw/d (BMD5)
Bitertanol	0.108	1.7	0.184	2.1	0.228
Cyproconazole	0.046	4.2	0.192	2.2	0.100
Diniconazole	0.038	0.6	0.023	1	0.038
Epoxiconazole	0.036	0.8	0.029	1.5	0.054
Flusilazole (IC)	0.037	1	0.037	1	0.037
Propiconazole	0.080	1.7	0.136	0.1	0.008
Triadimefon	0.224	1	0.224	1.2	0.269
Combined background exposure	-	-	**0.825**	-	**0.734**

Table 8 Combined background exposure of triazoles causing chronic effects (liver toxicity) for Dutch general population

Compound	Average chronic exposure		
	µg compound/kg bw/d	RPF (from NOAEL) for chronic effect	µg cyproconazole eq./kg bw/d (NOAEL)
Bitertanol	0.037	2.0	0.075
Cyproconazole (IC)	0.037	1.0	0.037
Difenoconazole	0.120	2.0	0.239
Diniconazole	0.031	0.4	0.012
Epoxiconazole	0.024	2.5	0.060
Flusilazole	0.038	4.0	0.150
Myclobutanil	0.113	0.05	0.006
Propiconazole	0.037	0.6	0.020
Tebuconazole	0.139	0.1	0.014
Triadimefon	0.070	0.1	0.007
Triadimenol	0.135	0.4	0.054
Combined background exposure	-	-	**0.674**

Table 9 Combined background exposure of triazoles causing chronic effects (liver toxicity) for Dutch children

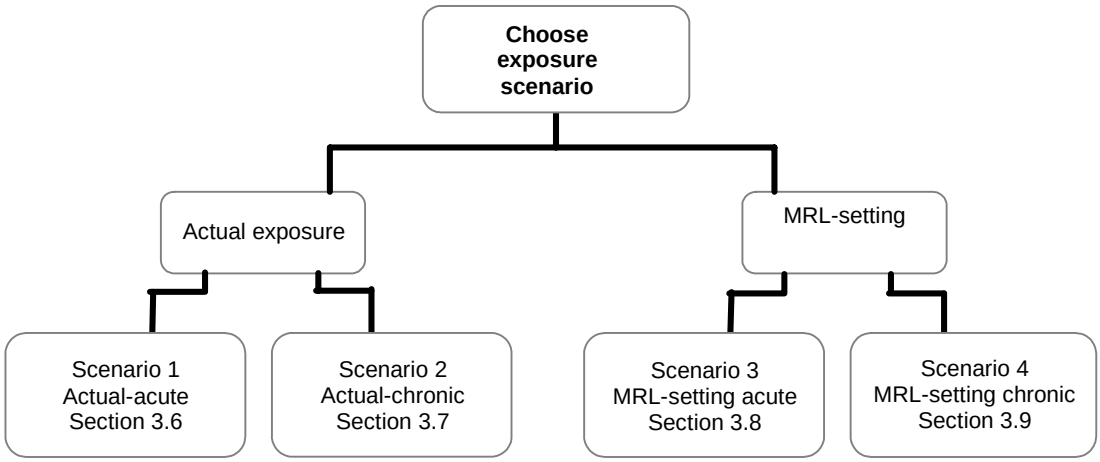
Compound	Average chronic exposure		
	µg compound/kg bw/d	RPF (from NOAEL) for chronic effect	µg cyproconazole eq./kg bw/d (NOAEL)
Bitertanol	0.108	2.0	0.219
Cyproconazole (IC)	0.046	1.0	0.046
Difenoconazole	0.311	2.0	0.623
Diniconazole	0.038	0.4	0.015
Epoxiconazole	0.036	2.5	0.090
Flusilazole	0.036	4.0	0.145
Myclobutanil	0.238	0.05	0.012
Propiconazole	0.080	0.6	0.048
Tebuconazole	0.349	0.1	0.035
Triadimefon	0.224	0.1	0.022
Triadimenol	0.379	0.4	0.151
Combined background exposure	-	-	**1.406**

3.5. Introduction of exposure assessment scenarios

In the following Sections (3.6 to 3.9), the exposure assessments for all four scenarios are described, both for the deterministic and the probabilistic tier.

Scenario 1 refers to the actual exposure (i.e. from the patterns of usage that actually occur in practice), during a short (i.e. 24 hours) time span; scenario 2 to the actual exposure during a chronic (i.e. lifetime) time span; scenario 3 to 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 scenario 4 to chronic (i.e. lifetime) exposure relevant for MRL-setting assessed at the level of the STMR. Figure 6 presents a guide through the scenarios.

Figure 6. **Guide to Sections 3.6 to 3.9**



3.6. Scenario 1: actual acute cumulative exposure assessment

This scenario addresses the actual exposure (i.e. from the patterns of usage that actually occur in practice), during an acute (i.e. 24 hours) time span (see 1.1). As stated in 1.3, it was proposed in the previous opinion that in estimating the actual cumulative exposure scenarios (both acute and chronic), residue levels from monitoring programmes should be used for all commodity/pesticide combinations in the assessment. Furthermore, since for an actual exposure assessment there is no emphasis on a specific commodity for which the MRL is proposed to be set but rather an interest in obtaining a complete picture of the usual intakes of consumers, the group of consumers considered should be the total population of interest (e.g. general population or children), i.e. including non-consumers of a certain commodity (since a consumer who didn't eat apples on the day of the survey might well have eaten some other fruits containing residues of interest and therefore should not be disregarded).

However, the PPR Panel noted that in the case of the actual acute cumulative exposure, two subscenarios can be identified:

1. Routine evaluation of all available monitoring data, regarding acute risks for consumers as explained in the above paragraph.

2. Enforcement situation; evaluation of individual samples.

In sub-scenario 2, the cumulative exposure estimations would focus on the group of consumers eating the commodity on which a high residue was found, and it is as such based on a different population ('consumers only') than sub-scenario 1.

The Panel noted that the first subscenario would be difficult to address by a deterministic model, since the number of individual calculations building up the assessment would be extremely large. Selecting the appropriate residue for each individual food item is difficult and would be arbitrary since a high residue should be included, but to select a high residue for every food item and every pesticide in the CAG would be an extreme worst-case. The deterministic approach can address isolated events of co-occurrence of 2 or more pesticides from the same CAG in a particular commodity like the critical commodity, or the commodity in which a residue exceeding the MRL was found, but does not give information on the probability of co-occurrence events in general.

In the deterministic approach described in 3.6.1, the cumulative exposure was estimated by the "critical commodity" concept using the consumption values in the PRIMo model for 'consumers only'. Thus, the

deterministic approach adopted by the Panel in this exercise addresses subscenario 2. However, in principle consideration could also be given to using this deterministic approach based on critical commodities as a pragmatic first tier for subscenario 1, provided it results in an appropriate degree of conservatism.

Regarding the use of a deterministic methodology in actual acute exposure assessment, the general opinion reported some experiences in the UK and Denmark. In these examples, the assessors identified cases where several compounds belonging to the same CAG were simultaneously present in the same commodity sampled from the market and performed cumulative risk assessment for consumers eating that commodity. To perform this exercise, the residue database needs to contain information of co-occurrence, meaning that each recorded monitoring sample must be kept associated with all related findings. A weakness of this approach is that it does not consider the contribution from combined background exposure (see 3.4) resulting from the consumption on the same day of multiple other commodities which may also contain residues of pesticides of the CAG.

The PPR Panel therefore opted for the other option - which in practice may be complementary to that performed in the UK and Denmark - consisting of determining, for each of the pesticides belonging to the CAG, the highest potential individual exposure event on the basis of the highest residue level found in each of the monitored commodities and adding it to a combined background exposure (average intake times average residue for all pesticide/commodity combinations, see 3.4). As co-occurrence data were not available for this exercise, the PPR Panel could not integrate this parameter into this assessment. This type of approach reflects subscenario 2 as its focuses on a particular residue (the one giving the highest exposure) combined with a 'consumer only' consumption value for this critical commodity.

The PPR Panel assumed that a reasonable representation of the background for actual acute cumulative exposure assessments would be given by the average cumulated chronic exposure to the 7 pesticides from the CAG for acute assessment.

3.6.1. Scenario 1: deterministic tiers actual_acute

As mentioned above, the deterministic approach under this scenario consisted of combining selected high exposure events (the most critical commodity for each pesticide) with the background exposure.

The details of the background exposure calculations were given under point 3.4, and this point deals with the determination of the contribution of high exposure events.

For each of the 7 pesticides of the acute CAG, all individual residue data have been scrutinized in order to determine the pesticide/commodity combination leading to the highest potential acute dietary intake. This was done in PRIMo using the appropriate IESTI equation in which the highest residue level found for each commodity in the monitoring programmes was used as the HR (Highest Residue) value.

Below are the IESTI equations; see WHO (1997b) for further background.

Case 1 (unit weight < 25g):

$$IESTI = \frac{LP \times (HR \; or \; HR\_P)}{bw}$$

Case 2 (unit weight > 25 g)**:**

- **Case 2a** (Unit weight < large portion):

$$IESTI = \frac{U \times (HR\ or\ HR\_P) \times v \quad + \quad (LP - U) \times (HR\ or\ HR\_P)}{bw}$$

- **Case 2b** (Unit weight > large portion):

$$IESTI = \frac{LP \times (HR\ or\ HR\_P) \times v}{bw}$$

Case 3 (Bulked or blended commodity):

$$IESTI = \frac{LP \times STMR\_P}{bw}$$

This allowed, for each pesticide, identification of the critical commodity that is the commodity causing the highest individual exposure from a LP size meal. The critical commodity/pesticide combinations for the Dutch population were identified as bitertanol/bananas, cyproconazole/table grapes, diniconazole/table grapes, epoxiconazole/leek, flusilazole/table grapes, propiconazole/broccoli, triadimefon/pineapples (general population) and triadimefon/table grapes (children).

The cumulative exposures were then calculated for each pesticide as the sum of the exposure from consumption of the LP size meal of the critical commodity and the RPF-transformed background exposure from all the other pesticide/commodities corrected for the background from the pesticide in the critical commodity.

Cumulative exposure $E_{\hat{\jmath},cum}$ for the specific pesticide $\hat{\jmath}$ by consumption of an LP size meal of the critical commodity $\hat{\imath}$:

$$E_{\hat{\jmath},cum} = E_{\hat{\imath},LP,\hat{\jmath}} + \left(\sum_{j=1}^{n_j} RPF_j * \left(\sum_{i=1}^{n_i} \left(I_i * C_{i,j} \right) \right) \right) - B_{\hat{\imath},\hat{\jmath}}$$

$\hat{J}$ = Specific pesticide

$E_{\hat{\imath},LP,\hat{\jmath}}$ = Exposure to the specific pesticide $\hat{\jmath}$ from consumption of an LP size meal of the critical commodity $\hat{\imath}$

I_j = Average daily intake of commodity j

$C_{i,j}$ = Average residue level of pesticide j in commodity i

RPF_j = Relative Potency Factor for pesticide j (see section 2.4)

$B_{\hat{\imath},\hat{\jmath}}$ = Background exposure to the specific pesticide $\hat{\jmath}$ in the critical commodity $\hat{\imath}$

The potential acute cumulative intake in high exposure events for each of the pesticides included in the CAG for acute effects is reflected in table 10 and 11.

Calculation methodology: EFSA PRIMo model

Input parameters:

Consumption data: Dutch LP consumption (corresponding to 97.5th percentile of the distribution) for general population (1-97 years) and population of children (1-6 years) from a 1997-8 dietary survey (Anonymous, 1998) for the relevant critical commodities. Dutch average long term consumptions for the other commodities.

Residue data: For high exposure events: bitertanol/bananas (0.52 mg/kg), cyproconazole/table grapes (0,08 mg/kg), diniconazole/table grapes (0,05 mg/kg), epoxiconazole/leek (0,05 mg/kg), flusilazole/table grapes (0,08 mg/kg), propiconazole/broccoli (0,35 mg/kg), triadimefon/pineapples, (1,3 mg/kg) and triadimefon/table grapes (0,2 mg/kg). For background see Chapter 3.4

Edible portion factor and processing factors: not applied due to lack of the relevant consumption data. Consequently, it was considered that all commodities were consumed entirely as raw commodities.

Variability factors and unit weights as given in the PRIMo Model. When PRIMo offered a choice concerning the value of the variability factor, the highest value was selected.

Table 10. Dutch general population: highest acute exposure events to each of the pesticide in the CAG for acute effects. In the columns giving the exposure as µg flusilazole eq./kg bw/d, first the exposure to the critical commodity is presented, and then, the cumulative exposure including the background is given in brackets.

Pesticide/commodity combination and monitoring level	Acute exposure				
	Expressed as µg compound/kg bw/d	RPF (from NOAEL)	µg flusilazole eq./kg bw/d (NOAEL)	RPF (from BMD5)	µg flusilazole eq./kg bw/d (BMD5)
bitertanol/bananas	7.7	1.7	13.0 (13.4)	2.1	16.1 (16.4)
cyproconazole/table grapes	2.5	4.2	10.7 (11.0)	2.2	5.6 (5.9)
diniconazole/table grapes	1.3	0.6	0.76 (1.2)	1	1.3 (1.6)
epoxiconazole/leek	0.8	0.8	0.61 (1.0)	1.5	1.2 (1.5)
flusilazole/table grapes	2.5	1	2.54 (2.96)	1	2.5 (2.8)
propiconazole/broccoli	7.5	1.7	12.7 (13.1)	0.1	0.8 (1.1)
triadimefon/pineapples	20.7	1	20.7 (21.1)	1.2	24.8 (25.1)

Table 11. Dutch children: highest acute exposure events to each of the pesticide in the CAG for acute effects. In the columns giving the exposure as µg flusilazole eq./kg bw/d, first the exposure to the critical commodity is presented, and then, the cumulative exposure including the background is given in brackets.

Pesticide/commodity combination and monitoring level (mg/kg)	Acute exposure				
	Expressed as µg compound/kg bw/d	RPF (from NOAEL)	µg flusilazole eq./kg bw/d (NOAEL)	RPF (from BMD5)	µg flusilazole eq./kg bw/d (BMD5)
bitertanol/bananas	27.9	1.7	47.4 (48.2)	2.1	58.6 (59.2)
cyproconazole/table grapes	4.7	4.2	19.7 (20.4)	2.2	10.3 (11.0)
diniconazole/table grapes	2.3	0.6	1.4 (2.2)	1	2.3 (3.0)
epoxiconazole/leek	1.7	0.8	1.4 (2.2)	1.5	2.5 (3.2)
flusilazole/table grapes	4.7	1	4.7 (5.5)	1	4.7 (5.4)
propiconazole/broccoli	10.9	1.7	18.5 (19.3)	0.1	1.1 (1.8)
triadimefon/table grapes	11.5	1	11.5 (12.3)	1.2	13.8 (14.5)

3.6.2. Scenario 1: probabilistic tier actual_acute

In addition to the deterministic calculations performed by the PPR Panel, probabilistic modelling was commissioned to the Rikilt Institute. These probabilistic calculations reflect subscenario 1. The RPF method was used to assess the actual acute cumulative exposure, using NOAEL- and BMD5-derived RPFs (van Klaveren et al., 2009).

A probabilistic MCRA model was used to produce the individual short term estimates. See 3.1 of the current opinion, and Sections 2.5 and 2.6 in van Klaveren et al, 2009, for further details on the methodology.

Input parameters:

Consumption data: Individual Dutch daily consumption records from a 1997-8 dietary survey (Anonymous 1998). Two probabilistic calculations were performed, one including all consumers (or all consumption-days) from the general population (1-97 years) and one involving all consumers (or all consumption-days) from the children subpopulation (1-6 years).

Residue data: Individual analytical results from Dutch monitoring exercises of 2002-2007. Information on possible co-occurrence of pesticides from the CAG in the same commodity was not available. All ND values were replaced by 0 (in contrast to the approach in the deterministic calculations, see Section 3.2.6). An extrapolation system was used for unmonitored commodities from monitored commodities having the same MRLs and belonging to the same extrapolation group (see 3.2.4).

Fixed variability factor of 3.6, which is the average variability factor calculated by the PPR Panel in monitoring samples in 2005 (EFSA, 2005).

Processing factors were applied when available from relevant DAR and JMPR evaluations. See Annex IV in van Klaveren et al. (2009).

Unit weight: see Annex V in van Klaveren et al. (2009).

A range of selected percentiles of estimated exposure is presented in Tables 12 and 13.

Table 12. Selected percentiles and mean level of estimated cumulative actual acute exposure of Dutch general population and children (RPFs based on NOAELs)

Country	Consumer group	Age range	Percentiles of estimated acute exposure µg equivalents of flusilazole/kg bw/day					
			95	97.5	99	99.9	99.99	Mean
NL	Dutch general	1 - 97	<0.1	0.1	0.2	1.3	5.2	0.01
NL	Dutch children	1 - 6	0.1	0.2	0.4	3.5	11.7	0.03

Wheat, banana and pineapple were found to be the 3 commodities with the highest contribution to the exposure accounting for approximately 80% of total cumulative exposure. The top 3 triazoles were found to be propiconazole, triadimefon and bitertanol, which accounted for more than 95% of the total cumulative exposure.

Table 13. Selected percentiles and mean level of estimated cumulative actual acute exposure of Dutch general population and children (RPFs based on BMD5s)

Country	Consumer group	Age range	Percentiles of estimated acute exposure µg equivalents of flusilazole/kg bw/day					
			95	97.5	99	99.9	99.99	Mean
NL	Dutch general	1 - 97	<0.1	0.1	0.2	1.5	6.4	0.01
NL	Dutch children	1 - 6	0.1	0.2	0.5	4.0	14.9	0.03

The top two commodities contributing most to the estimated exposures of Dutch consumers were found to be pineapple and banana, while the third was tomato for the total population and apple for children. The top 3 commodities accounted for approximately 80% of the total cumulative acute exposure of Dutch consumer groups. Bitertanol, triadimefon and propiconazole were the major contributors accounting for more than 95% of the overall estimated cumulated acute exposure of the two Dutch consumer groups.

3.7. Scenario 2: actual chronic cumulative exposure assessment

This scenario addresses the actual exposure (i.e. from the patterns of usage that actually occur in practice), during a chronic (i.e. lifetime) time span (see 1.1). As stated in 1.3, it was proposed in the previous opinion that in estimating the actual cumulative exposure scenarios (both acute and chronic), residue levels from monitoring programmes should be used for all commodity/pesticide combinations in the assessment. Furthermore, since for an actual exposure assessment there is no emphasis on a specific commodity for which the MRL is proposed to be set, but rather an interest in obtaining a complete picture of the usual intakes of consumers, the group of consumers considered should be the total population of interest (e.g. general population, or children), i.e. including non-consumers of a certain commodity

(since a consumer who didn't eat apples on the day of the survey might well have eaten some other fruits containing residues of interest, and therefore should not be disregarded). In contrast with Scenario 1, isolated high exposure events are not of toxicological significance and do not impact long term risk assessments. For this reason, actual chronic exposure assessment requires only information reflecting the overall average residue pattern to which the consumer is exposed.

This scenario can be addressed by both deterministic and probabilistic methodologies in a tiered approach.

3.7.1. Scenario 2: deterministic tiers actual_chronic

As recommended in the previous opinion of the PPR Panel, the residue levels from monitoring programmes have been used for all pesticide/commodity combinations. Consumption data were used as present in PRIMo.

The calculations included the 11 pesticides for which liver effects were considered the common effect.

Regarding the consumption data, the EFSA PRIMo model currently uses mean consumption figures which are collected from the EU Member States. The mean values are preferred as they better reflect the food consumption habits and not the day-to-day variation, which allows for a comparison with the relevant toxicological threshold (i.e. the ADI), which is based on intake over a lifetime (EFSA, 2007a). These values are used in the TMDI and IEDI equations as formulated by WHO (1997a) and as used by the Codex Alimentarius (JMPR). However, there is an important difference in the kind of consumption data available to Codex, and to EFSA. Codex uses for the chronic intake calculations consumption values derived from FAO Food Balance Sheets, which are essentially the sum of what is grown a country and what is imported, minus what is exported, and then divided by the number of inhabitants. It is generally known that these values represent an overestimation of the consumption, so it is not really a 'mean' consumption.

When truly mean consumption values are addressed, as in PRIMo, one may argue that a person consuming a higher than average portion might not be sufficiently taken into account. In MRL-setting scenarios however (for which PRIMo was established), this is compensated by the fact, that all commodities are assumed to contain a residue concentration at the STMR, for every meal that is eaten over a life-time (note that in the TMDI and IEDI equations, intakes are summed over all relevant commodities). It should be noted that it has never been investigated whether the underestimation on the consumption side balances out the overestimation on the residue concentration side, but all in all this approach is workable. However, when the aim is to calculate an actual chronic, cumulative exposure, and mean concentrations from monitoring data are used, it is questionable whether this balance is still valid.

The PPR Panel decided, for the sake of the worked example, to do the calculations as proposed by using the PRIMo. By direct comparison with the probabilistic calculations, conclusions can be drawn as to whether this approach is a true first tier, or not.

The input parameters and results for this scenario have been described in Chapter 3.4, as the combined actual chronic exposure represents the background exposure used in the MRL setting-scenario (Table 8 and 9). These parameters and the results of the calculations will therefore not be reproduced here.

3.7.2. Scenario 2: probabilistic tier actual_chronic

In addition to the deterministic calculations performed by the PPR Panel, probabilistic modelling was commissioned to the Rikilt Institute. In order to assess the actual chronic combined exposure, distributions of long term cumulative intakes were provided using the NOAEL-derived RPF methods (van Klaveren et al., 2009).

A probabilistic MCRA model was used to produce the individual long term estimates. See 3.1 in the current opinion, and sections 2.5 and 2.6 in van Klaveren et al, 2009, for further details on the methodology.

Input parameters:

Consumption data: Individual Dutch daily (short-term) consumption records from a 1997-8 dietary survey (Anonymous, 1998), transformed to usual intake distributions by the ISUF model, see van Klaveren et al. (2009), Section 2.5. Two probabilistic calculations were performed, one including all consumers (or all consumption-days) from the general population (1-97 years) and one involving all consumers (or all consumption-days) from the children subpopulation (1-6 years).

Residue data: average residue level of each compound of the CAG in each food commodity, as derived from Dutch monitoring exercises of 2002-2007. Information on possible co-occurrence of pesticides from the CAG in the same commodity was not available. All non-detect values were replaced by 0. An extrapolation system was used for unmonitored commodities from monitored commodities having the same MRLs and belonging to the same extrapolation group.

Processing factors were applied when available from relevant DAR and JMPR evaluations.

A range of selected percentiles of estimated exposure is presented in tables 14 and 15.

Table 14. Selected percentiles and mean level of estimated cumulative chronic exposure of Dutch general population and children (RPFs based on NOAELs)

Country	Consumer group	Age range	Percentiles of estimated chronic exposure µg equivalents of cyproconazole/kg bw/day					
			95	97.5	99	99.9	99.99	Mean
NL	Dutch general	1 - 97	<0.1	0.1	0.1	0.1	0.1	0.02
NL	Dutch children	1 - 6	0.1	0.1	0.2	0.3	0.3	0.04

Bananas, pineapple and wheat (general population) or apples (children) were found to be the 3 commodities with the highest contribution to the exposure accounting for approximately 50% and 60% of total cumulative exposure in general and children populations respectively. The top 3 triazoles were found to be bitertanol, triadimenol and difenoconazole, which accounted for more than 70% of the total cumulative chronic exposure in both populations.

3.8. Scenario 3: acute cumulative exposure assessment_MRL-setting

Under this scenario, the acute (i.e. 24 hours) cumulative exposure relevant for MRL-setting (i.e. a theoretical exposure where the residue of the commodity/pesticide combination under evaluation is at the level of the MRL), is addressed (see 1.1).

Furthermore, the group of consumers considered should only be those who consume the commodity of interest. This type of selection is also called the 'eaters only' or 'consumers only' approach and contrasts with the approach for estimating the actual acute cumulative exposure for which all individuals are included. For all other commodity/pesticide combinations in the assessment, background levels (e.g., from monitoring programmes) should be used (see 1.3)

The aim of the MRL-setting scenarios is to ascertain that the residue level that will be adopted in the legislation is a safe level.

To exemplify the procedure, the cumulative exposures for MRL-settings were estimated for a set of commodity/ pesticide combinations. These include bitertanol, cyproconazole, diniconazole and epoxiconazole that are 4 of the 7 triazoles in the acute CAG. The selected commodity/ pesticide combinations are summarised in table 15 below. These combinations were selected so that they involved several plant commodities which, for the purposes of the exercise, preferably lead to high potential exposures at short and long term (considering the related consumption and MRL levels).

Table 15. Selected pesticide/commodity combinations for exposure and risk assessment with regard to MRL-setting

Residue	**Bitertanol**			**Cyproconazole**			**Diniconazole**	**Epoxiconazole**	
Commodity	Apple	Banana	Tomato	Table Grapes	Lettuce	Peach	Table grapes	Cabbage	Wheat

3.8.1. Scenario 3: deterministic tiers MRL-setting_acute

The setting of MRL-values for a pesticide can involve one or several commodities. Similar to the common practice of single pesticide assessment, cumulative exposure assessments were considered separately for each of the selected commodity/ pesticide combinations.

In its previous opinion on cumulative risk assessment (EFSA, 2008a), the PPR Panel defined the cumulative acute exposure in the MRL setting scenario as the sum of the contribution of the considered commodity/ pesticide combination and of background exposure.

Under point 3.4, the calculation of the background exposure was presented. In 3.6.1, the IESTI equations are described, yielding the value for Ex,LP.

The cumulative exposures were then calculated for each pesticide as the sum of the exposure from consumption of the LP size meal of the selected pesticide/commodity combination at the MRL level and the background from all the other pesticide/commodities except the background from the pesticide/commodity combination at the MRL level.

Acute cumulative exposure $E_{\hat{\jmath},cum}$ for the specific pesticide $\hat{\jmath}$ at MRL-level in the commodity $\tilde{\imath}$:

$$E_{\hat{\jmath},cum} = E_{\tilde{\imath},LP,\hat{\jmath},MRL} + \left(\sum_{j=1}^{n_j} RPF_j * \left(\sum_{i=1}^{n_i} I_i * C_{i,j} \right) \right) - B_{\tilde{\imath},\hat{\jmath}}$$

$E_{\tilde{\imath},LP,\hat{\jmath},MRL}$ = Exposure to the specific pesticide $\hat{\jmath}$ at MRL-level from consumption of an LP size meal of the commodity $\tilde{\imath}$

I_i = Average daily intake of commodity i

$C_{i,j}$ = Average residue level of pesticide j in commodity i

RPF_j = Relative Potency Factor for pesticide j (see section 2.4)

$B_{\tilde{\imath},\hat{\jmath}}$ = Background exposure to the specific pesticide $\hat{\jmath}$ in the commodity $\tilde{\imath}$

Input parameters:

Consumption data: Dutch Large Portion consumption (corresponding to 97.5th percentile of the distribution) for general population (1-97 years) and population of children (1-6 years) from a 1997-8 dietary survey (Anonymous, 1998) for the commodity under consideration. Dutch long term consumptions for the other commodities.

Residue data: MRL level for the above-mentioned 9 pesticide/commodity combinations.

Edible portion factor and processing factors: not applied due to lack of relevant consumption data. Consequently, it was considered that all commodities were consumed entirely as raw commodities.

Variability factors and unit weights as given in the PRIMo Model. Highest value of variability factor has been used, when PRIMo offered a choice of more than one value.

Under these assumptions, the potential consumer acute intake at MRL level for each of the pesticide/commodity combinations under consideration is reflected in Tables 16 and 17.

Table 16. Dutch general population: acute intake for each of the pesticide/commodity combinations at the respective MRL level. In the columns giving the exposure as µg flusilazole eq./kg bw/d, first the exposure to the pesticide/commodity combination at the MRL-level is presented, and then, between brackets, the total exposure including the background.

Pesticide/commodity combination and MRL level	Acute exposure				
	Expressed as µg compound/kg bw/d	RPF (from NOAEL)	µg flusilazole eq./kg bw/d (NOAEL)	RPF (from BMD5)	µg flusilazole eq./kg bw/d (BMD5)
Bitertanol/apples (2 mg/kg)	35.1	1.7	59.7 (60.1)	2.1	73.7 (74.1)
Bitertanol/tomatoes (3mg/kg)	40.2	1.7	68.3 (68.8)	2.1	84.4 (84.8)
Bitertanol/bananas (3 mg/kg)	44.2	1.7	75.1 (75.5)	2.1	92.7 (93.1)
Cyproconazole/table grapes (0.2 mg/kg)	6.3	4.2	26.7 (27.1)	2.2	14.0 (14.3)
Cyproconazole/lettuce (0.05 mg/kg)	0.5	4.2	2.0 (2.4)	2.2	1.1 (1.4)
Cyproconazole/peach (0.2 mg/kg)	1.8	4.2	7.6 (8.0)	2.2	4.0 (4.3)
Diniconazole/table grapes (0.2 mg/kg)	6.4	0.6	3.8 (4.2)	1	6.4 (6.7)
Epoxiconazole/cabbage (0.2 mg/kg)	6.6	0.8	5.3 (5.7)	1.5	9.9 (10.3)
Epoxiconazole/wheat (0.2 mg/kg)	0.6	0.8	0.5 (0.9)	1.5	0.9 (1.3)

Table 17. Dutch children: acute intake for each of the pesticide/commodity combinations at the respective MRL level. In the columns giving the exposure as µg flusilazole eq./kg bw/d, first the exposure to the pesticide/commodity combination at the MRL-level is presented, and then, between brackets, the total exposure including the background.

Pesticide/commodity combination and MRL level (mg/kg)	Acute exposure				
	Expressed as µg compound/kg bw/d	RPF (from NOAEL)	µg flusilazole eq./kg bw/d (NOAEL)	RPF (from BMD5)	µg flusilazole eq./kg bw/d (BMD5)
Bitertanol/apples (2 mg/kg)	123.0	1.7	209.1 (209.9)	2.1	258.3 (259.0)
Bitertanol/tomatoes (3mg/kg)	94.5	1.7	160.7 (161.5)	2.1	198.5 (199.2)
Bitertanol/bananas (3 mg/kg)	160.5	1.7	272.9 (273.7)	2.1	337.1 (337.8)
Cyproconazole/table grapes (0.2 mg/kg)	11.6	4.2	48.9 (49.7)	2.2	25.6 (26.3)
Cyproconazole/lettuce (0.05 mg/kg)	1.1	4.2	4.5 (5.4)	2.2	2.4 (3.1)
Cyproconazole/peach (0.2 mg/kg)	5.3	4.2	22.2 (23.0)	2.2	11.6 (12.4)
Diniconazole/table grapes (0.2 mg/kg)	11.7	0.6	7.0 (7.8)	1	11.7 (12.4)
Epoxiconazole/cabbage (0.2 mg/kg)	10.8	0.8	8.6 (9.5)	1.5	16.2 (16.9)
Epoxiconazole/wheat (0.2 mg/kg)	1.8	0.8	1.4 (2.3)	1.5	2.7 (3.4)

3.8.2. Scenario 3: probabilistic tier MRL-setting acute

In addition to the deterministic calculations performed by the PPR Panel, probabilistic modelling was commissioned to the Rikilt Institute. Distributions of short term cumulative intakes were provided using both the NOAEL- and BMD5-derived RPFs (van Klaveren et al., 2009) for each of the selected pesticide/commodity combinations.

A probabilistic MCRA model was used to produce the individual short term estimates. See 3.1 of the current opinion, and sections 2.5 and 2.6 in van Klaveren et al. (2009), for further details on the methodology.

Input parameters:

Consumption data: Individual Dutch daily (short-term) consumption records from a 1997-8 dietary survey (Anonymous, 1998). Two probabilistic calculations were performed, one including effective consumers (consumption-days above 0 only) from the general population (1-97 years) and one involving effective consumers (consumption-days above 0 only) from the children subpopulation (1-6 years).

Residue data: For the considered pesticide/commodity combination, the MRL level was used. For all other pesticide/commodity combinations, the individual analytical results from monitoring exercises in 7 countries (Czech Republic, Finland, Italy, Sweden, The Netherlands, France and the United Kingdom) ranging from 2002 to 2007were used. Information on possible co-occurrence of pesticide from the CAG in the same commodity was not available. All ND values were replaced by 0. An extrapolation system was used for unmonitored commodities from monitored commodities having the same MRLs and belonging to the same extrapolation group.

Processing factors were applied when they were available from relevant DAR and JMPR evaluations (see Annex IV in van Klaveren et al., 2009).

A fixed variability factor of 3.6 was used, which is the average variability factor calculated by the PPR Panel in monitoring samples in 2005 (EFSA, 2005).

Major results of this probabilistic modelling are given in Tables 18 and 19.

Table 18. Selected percentiles and mean level of estimated cumulative acute exposure of the general Dutch population and children (RPFs based on NOAELs) for the selected pesticide/commodity combinations at the respective MRL level.

Commodity (MRL mg/kg)	Consumer group	Age range	Percentiles of estimated acute exposure µg equivalents of flusilazole/kg bw/day					
			95	97.5	99	99.9	99.99	Mean
Bitertanol/Apple (2 mg/kg)	Dutch total	1 - 97	17.6	25.2	38.1	88.0	171.1	4.2
Bitertanol/Apple (2 mg/kg)	Dutch children	1 - 6	38.5	53.9	77.3	158.3	280.9	8.6
Bitertanol/Banana (3 mg/kg)	Dutch total	1 - 97	13	19.8	31.8	75.8	144.4	3.0
Bitertanol/Tomato (3 mg/kg)	Dutch total	1 - 97	26.2	41.0	67.3	164.6	257.0	6.2
Bitertanol/Tomato (3 mg/kg)	Dutch children	1 - 6	56.2	81.0	161.5	257.0	257.9	11.8
Cyproconazole/table grapes (0.2 mg/kg)	Dutch children	1 - 6	4.5	7.2	12.1	35.7	89.2	0.9
Cyproconazole/lettuce (0.05 mg/kg)	Dutch children	1 - 6	1.6	2.1	2.9	5.7	9.9	0.5
Cyproconazole/peach (0.2 mg/kg)	Dutch children	1 - 6	0.5	0.9	1.8	7.4	17.6	0.1
Epoxiconazole/cabbage (0.2 mg/kg)	Dutch children	1 - 6	1.7	2.5	3.7	8.4	16.9	0.4
Epoxiconazole/wheat (0.2 mg/kg)	Dutch total	1 - 97	0.8	1.0	1.2	2.3	5.7	0.3

Table 19. Selected percentiles and mean level of estimated cumulative acute exposure of the Dutch general population and children (RPFs based on BMD5s) for the selected pesticide/commodity combinations at respective MRL level.

Pesticide/Commodity combination	Consumer group	Age range	Percentiles of estimated acute exposure µg equivalents of flusilazole/kg bw/day					
			95	97.5	99	99.9	99.99	Mean
Bitertanol/Apple (2 mg/kg)	Dutch total	1 - 97	21.7	31.3	47.3	112.6	211.9	5.2
Bitertanol/Apple (2 mg/kg)	Dutch children	1 - 6	47.7	66.6	95.3	196.3	345.1	10.6
Bitertanol/Banana (3 mg/kg)	Dutch total	1 - 97	15.9	24.3	39.1	93.8	176.2	3.7
Bitertanol/Tomato (3 mg/kg)	Dutch total	1 - 97	32.3	50.7	83.1	202.9	317.5	7.6
Bitertanol/Tomato (3 mg/kg)	Dutch children	1 - 6	68.5	99.2	199.3	317.5	317.7	14.5
Cyproconazole/table grapes (0.2 mg/kg)	Dutch children	1 - 6	2.4	3.9	6.5	18.4	45.6	0.5
Cyproconazole/lettuce (0.05 mg/kg)	Dutch children	1 - 6	0.9	1.2	1.7	3.9	9.1	0.3
Cyproconazole/peach (0.2 mg/kg)	Dutch children	1 - 6	0.3	0.6	1.3	5.7	16.2	0.1
Epoxiconazole/cabbage (0.2 mg/kg)	Dutch children	1 - 6	3.1	4.5	6.8	15.4	29.7	0.8
Epoxiconazole/wheat (0.2 mg/kg)	Dutch total	1 - 97	1.4	1.7	2.1	3.4	7.5	0.6

Estimated exposure levels calculated using RPFs derived from NOAELs were in general slightly lower than those based on RPFs derived from BMDs for the MRL setting scenarios for bitertanol. This reflects the fact that the RPF for bitertanol is 1.7 when based on the NOAEL and 2.1 when based on the BMD, respectively. The opposite is found in MRL setting scenarios for cyproconazole. For MRL setting of this pesticide in peach, the 99.9 percentile exposure level for Dutch children is estimated to be 7.4 and 5.7 µg equivalents of flusilazole/kg bw/d using RPFs derived from NOAEL and BMD, respectively. Again this reflects the respective RPFs, which are 4.2 when derived from the NOAEL and 2.2 when derived from the BMD. See section 6.1.3 for discussion on NOAEL and BMD derived RPFs.

The contribution of the commodities and pesticides to the overall cumulative estimated exposure to triazoles for selected combinations were also calculated using both the NOAEL and BMD derived RPFs. In all scenarios the commodity/pesticide combination for which the MRL value was used as input for the exposure estimation contributed the most to the total intake. For the MRL setting scenarios for bitertanol the exposure levels based on NOAEL-derived RPFs were relatively high e.g. the 99.9 percentile for children varied between 110.7 and 257.0 µg equivalents of flusilazole/kg bw/d. The MRL of 2 mg/kg is approximately a factor 1000 to 2000 higher than the monitoring results for the other triazole pesticides, but in many cases the ratio between the MRL and the monitoring results is much smaller. The MRL proposed for cyproconazole in peaches is 0.1 mg/kg and a typical monitoring value is 0.03 mg/kg. In such cases the contribution of other RAC-pesticide combinations to the total estimated average exposure levels is much greater.

3.9. Scenario 4: chronic cumulative exposure assessment_MRL-setting

Under this scenario, the chronic (i.e. lifetime) 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 STMR) is addressed (see 1.1).

With regard to chronic cumulative risk assessment for MRL-setting, it was noted that although for assessments of single chemicals, the assumption is that in the worst case, consumption could be at the MRL (or Supervised Trial Median Residue (STMR)) for all commodities of interest over a lifetime, this assumption would be very unrealistic for a cumulative assessment. It was concluded though that as a first tier, an assessment combining lifetime exposure at the STMR for a given commodity/pesticide combination with background exposure (as derived from monitoring programmes) for all other commodities/pesticides could be performed.(see 1.3)

See Section 3.7.1 for discussion on the consumption data available in PRIMo.

The pesticide/commodity combinations that were addressed for this scenario are listed in table 20, with the respective information regarding STMR levels.

Table 20. STMR values for selected pesticide/commodity combinations

Pesticide/commodity combination	MRL (mg/kg)	Field Trial data (mg/kg)	Supervised Trials Median Residue (mg/kg)
Bitertanol/apple	2	0.08; 0.09; 0.09; 0.12; 0.12; 0.15; 0.16; 0.18; 0.23; 0.24; 0.34	0.15
Bitertanol/banana	3	0.06; 0.06; 0.1; 0.24; 0.32; 0.36	0.17
Bitertanol/tomato	3	0.39; 0.41; 0.48; 0.54; 0.56; 0.96; 0.96; 0.98; 2.1; 2.4	0.76
Epoxiconazole/wheat	0.2	<0.01; <0.01; 0.03; 0.04; <0.05; <0.05; <0.05; <0.05; <0.05; 0.1	0.05

3.9.1. Scenario 4: deterministic tiers MRL-setting_chronic

In its previous opinion on cumulative risk assessment, the PPR Panel defined the combined chronic exposure in the MRL setting scenario as the sum of the contribution of the considered pesticide/commodity combination at the STMR level and that of the background exposure[13].

Under point 3.4, the calculation of the background exposure was presented.

This point summarises how the contribution of the pesticide/commodity combinations under consideration was calculated. For each of the selected pesticide/commodity combinations, the chronic cumulative exposure assessments were performed according to the following calculation:

Exposure ($E_{\tilde{\imath},\hat{\jmath},STMR}$) to a specific pesticide $\hat{\jmath}$ by consumption of the commodity $\tilde{\imath}$ for which the residue concentration is at STMR-level :

$$E_{\tilde{\imath},\hat{\jmath},STMR} = I_{\tilde{\imath}} * C_{\tilde{\imath},\hat{\jmath},STMR}$$

$I_{\tilde{\imath}}$ = Average daily intake of commodity $\tilde{\imath}$

$C_{\tilde{\imath},\hat{\jmath},STMR}$ = Residue concentration of the specific pesticide $\hat{\jmath}$ at STMR-level in commodity $\tilde{\imath}$

[13] Since STMR-values were only available for a few pesticide/commodity combinations, the calculations were also performed using the level of the MRL, see Appendix K, highlighting the conclusion in the previous opinion that using the MRL would be a very conservative approach.

The cumulative exposure, $E_{\hat{\jmath},STMR,cum}$ is then found by summing up the contributions from pesticide $\hat{\jmath}$ at STMR-level in the commodity $\tilde{\imath}$ and the background exposure to all other pesticide/commodity combinations (j/i) corrected for the background from the pesticide $\hat{\jmath}$ in commodity $\tilde{\imath}$ for which the MRL is being assessed:

$$E_{\hat{\jmath},STMR,cum} = E_{\tilde{\imath},\hat{\jmath},STMR} + \left(\sum_{j=1}^{n_j} (RPF_j) * \left(\sum_{i=1}^{n_i} (I_i * C_{i,j}) \right) \right) - B_{\tilde{\imath},\hat{\jmath}}$$

I_i = Average daily intake of commodity i

$C_{i,j}$ = Average residue level of pesticide j in commodity i

RPF_j = Relative Potency Factor for pesticide j (see section 2.4)

$B_{\tilde{\imath},\hat{\jmath}}$ = Background exposure from the specific pesticide $\hat{\jmath}$ in commodity $\tilde{\imath}$

Calculation methodology: EFSA PRIMo model

Input parameters:

Consumption data: Dutch average long-term consumption of the general (1-97 years) and children populations (1-6 years) from a 1997-8 dietary survey (Anonymous, 1998).

Residue data: Respective STMR level for each of the selected pesticide/commodity combination (Table 20).

Edible portion factor and processing factors: not applied because the consumption data in PRIMo are all calculated back to RAC. Therefore it was not possible to combine a residue in processed food (derived from the residue in the RAC times the processing factor) with the appropriate consumption value. Consequently, it was considered that all commodities were consumed entirely as raw commodities.

Under these assumptions, the potential actual chronic intake at STMR level for each of the pesticide/commodity combinations is summarised in table 21 and 22 for the Dutch general population and children respectively.

Table 21. Dutch general population: chronic intake for each of the pesticide/commodity combinations at STMR level. In the column giving the exposure as µg cyproconazole eq./kg bw/d, first the exposure to the pesticide/commodity combination at the STMR-level is presented, and then, between brackets, the total exposure including the background.

Pesticide/commodity combination and STMR level	Chronic exposure		
	Expressed as µg compound/kg bw/d	RPF (from NOAEL)	Expressed as µg cyproconazole eq./kg bw/d
Bitertanol/apple (0.15 mg/kg)	0.18	2.0	0.35 (1.03)
Bitertanol/banana (0.17 mg/kg)	0.053	2.0	0.11 (0.78)
Bitertanol/tomato (0.76 mg/kg)	0.33	2.0	0.65 (1.32)
Epoxiconazole/wheat (0.05 mg/kg)	0.10	2.5	0.26 (0.93)

Table 22. Dutch children: chronic intake for each of the pesticide/commodity combinations at STMR level. In the column giving the exposure as µg cyproconazole eq./kg bw/d, first the exposure to the pesticide/commodity combination at the STMR-level is presented, and then, between brackets, the total exposure including the background.

Pesticide/commodity combination and STMR level	Chronic exposure		
	Expressed as µg compound/kg bw/d	RPF (from NOAEL)	Expressed as µg cyproconazole eq./kg bw/d
Bitertanol/apple (0.15 mg/kg)	0.95	2.0	1.9 (3.3)
Bitertanol/banana (0.17 mg/kg)	0.29	2.0	0.58 (2.0)
Bitertanol/tomato (0.76 mg/kg)	0.47	2.0	0.95 (2.4)
Epoxiconazole/wheat (0.05 mg/kg)	0.24	2.5	0.59 (2.0)

3.9.2. Scenario 4: probabilistic tier MRL-setting_chronic

In addition to the deterministic calculations performed by the PPR Panel, probabilistic modelling was commissioned to the Rikilt Institute. Distribution of long-term cumulative intakes was obtained using the NOAEL-based RPF method (van Klaveren et al., 2009) for each of the selected pesticide/commodity combinations.

A probabilistic MCRA model was used to produce 100.000 individual long term estimates. See 3.1 of the current opinion, and sections 2.5 and 2.6 in van Klaveren et al, 2009, for further details on the methodology.

Input parameters:

Consumption data: Individual Dutch daily (short-term) consumption records from a 1997-8 dietary survey (Anonymous, 1998), transformed to usual intake distributions by the ISUF model, see van Klaveren et al. (2009), Section 2.5. Two probabilistic calculations were performed, one including all consumers (or all consumption-days) from the general population (1-97 years) and one involving all consumers (or all consumption-days) from the child subpopulation (1-6 years).

Residue data: For the considered pesticide/commodity combination, the field trial data from which the STMR level was derived for deterministic calculations were used (Table 20). In case of trials leading to non quantifiable residues, the LOQ value was assigned. For all other combinations, the average residue level of each compound of the CAG in each food commodity, based on the monitoring results in 7 countries (Czech Republic, Finland, Italy, Sweden, The Netherlands, France and the United Kingdom) ranging from 2002 to 2007 was used. Information on possible co-occurrence of pesticides from the CAG in the same commodity was not available. All ND values were replaced by 0. An extrapolation system was used for unmonitored commodities from monitored commodities having the same MRLs and belonging to the same extrapolation group.

Processing factors were applied when available from relevant DAR and JMPR evaluations.

Major results of this probabilistic modelling are given in Table 23.

Table 23. Selected percentiles and mean levels of estimated cumulative chronic exposure of Dutch general population and children (RPFs based on NOAEL) for the selected pesticide/commodity combinations based on field trial data

Commodity	Consumer group	Age range	Percentiles of estimated chronic cumulative exposure µg equivalents of cyproconazole/kg bw/day					
			90	95	99	99.9	99.99	Mean
Bitertanol/Apple	Dutch total	1 - 97	0.9	1.2	2.1	3.4	3.7	0.3
Bitertanol/Apple	Dutch children	1 - 6	3.7	4.7	7.0	8.5	8.7	1.5
Bitertanol/Banana	Dutch total	1 - 97	0.2	0.3	0.8	1.3	1.4	0.1
Bitertanol/Tomato	Dutch total	1 - 97	1.5	1.9	3.1	4.4	4.7	0.7
Bitertanol/Tomato	Dutch children	1 - 6	2.5	3.3	5.2	6.5	6.6	1.1
Epoxiconazole/wheat	Dutch total	1 - 97	0.4	0.4	0.6	0.8	0.8	0.2
Epoxiconazole/wheat	Dutch children	1 - 6	0.7	0.8	1.1	1.2	1.3	0.5

Using field trial data of a particular commodity-pesticide combination as input in the long-term cumulative exposure calculations also resulted in an increase in estimated exposure levels compared to using only monitoring data, although less pronounced than for the acute calculations.

When examining comparable subpopulations like adults, the estimated exposure between countries was comparable. For example, the 99.9 percentile level of estimated exposure in the apple – bitertanol scenario for the cumulative exposures was 3.4 µg equivalents cyproconazole/kg bw/d for Dutch consumers and comparable to consumers from other countries (see van Klaveren et al., 2009).

When examining the contribution of commodities and pesticides to the estimated long-term exposure for the different scenarios, countries and subpopulations, the largest contributions originated in the majority of cases from the commodity-pesticide combinations for which field trial data were used instead of monitoring data (Annex 8 in van Klaveren et al., 2009). The contributions ranged from 75.3 to 98.6% for the scenarios in which field trial data for bitertanol were used (see Annex 8 in van Klaveren et al., 2009). The field trial data for bitertanol is relatively high compared to the monitoring data for bitertanol. In other scenarios, e.g. when field trial data for cyproconazole in lettuce were used as input, other and more commodity-pesticide combinations contributed to the total exposure in comparable percentages.

3.10. Evaluation of the calculation methods used to estimate the background exposure in the deterministic models

For scenario 1 (actual acute) the PPR Panel assumed that a reasonable representation of the background exposure would be given by the average cumulated chronic exposure to the 7 pesticides from the CAG for acute assessment. This was calculated using exactly the same mathematical procedure as for the determination of the actual chronic exposure, meaning that average daily intakes are multiplied by average residue levels, and summed. When calculating the average residue levels, residues <LOR were assumed to be at 1/2LOR in samples of commodities with detectable residues in one or more samples but at 0 in all samples of commodities without any detectable residues. See Section 3.4.

In Tables 24 and 25 the estimated cumulative acute exposures of Dutch consumers (NL-general) and of Dutch children (NL-child) are compared to the background exposures. The tables give the estimates of

the acute exposure from consumption of a LP-size meal of the critical commodity together with the background exposures from all the individual pesticides with and without contribution from the critical commodity.

The results indicate that the background exposure from all commodities except the critical one is in the order of 1 – 2 % of the acute exposure from consumption of a LP size meal of the critical commodity. It should be noted however, that the background exposure is itself a distribution. It is not clear where the calculated background exposure ends up in this distribution, and whether this level provides the desired level of protection. Therefore, the method for calculating the background should be further explored.

Table 24. Acute exposures of Dutch general population by consumption of critical commodity – for explanation see Section 3.6.

Residue	Critical Commodity	Acute exposure to selected residue from consumption of LP size meal of critical commodity	Background exposure to residue from all commodities except the critical commodity	Background exposure to residue from all commodities incl. the critical commodity
		µg/kg bw/day	µg/kg bw/day	µg/kg bw/day
Bitertanol	**Bananas**	7.7	0.028	0.037
Cyproconazole	**Table grapes**	2.5	0.032	0.037
Diniconazole	**Table grapes**	1.3	0.025	0.031
Epoxiconazole	**Leek**	0.8	0.019	0.024
Flusilazole	**Table grapes**	2.5	0.031	0.038
Propiconazole	**Broccoli**	7.5	0.035	0.037
Triadimefon	**Pineapples**	20.7	0.061	0.070

Table 25. Acute exposures of Dutch children by consumption of critical commodity – for explanation see Section 3.6.

Residue	Critical Commodity	Acute exposure to selected residue from consumption of LP size meal of critical commodity	Background exposure to residue from all commodities except the critical commodity	Background exposure to residue from all commodities incl. the critical commodity
		µg/kg bw/day	µg/kg bw/day	µg/kg bw/day
Bitertanol	**Bananas**	27.9	0.060	0.108
Cyproconazole	**Table grapes**	4.7	0.027	0.046
Diniconazole	**Table grapes**	2.3	0.019	0.038
Epoxiconazole	**Leek**	1.7	0.030	0.036
Flusilazole	**Table grapes**	4.7	0.017	0.037
Propiconazole	**Broccoli**	10.9	0.074	0.080
Triadimefon	**Table grapes**	11.5	0.205	0.224

The Panel decided to use the average background level for chronic effects as the actual chronic exposure addressed in scenario 2. As stated in Section 3.7.1, it should be further explored whether or not this yields the desired level of protection. See also Sections 6.2.1 and 6.4 for discussion.

For scenario 3 (acute MRL-setting), the same consideration applies as stated above for scenario 1. Therefore, also in this case the method for calculating the background should be further explored.

In scenario 4 (chronic MRL-setting), again, like for scenario 2, it should be further discussed whether or not a background level based on average consumptions provides a sufficient level of protection.

4. Cumulative risk characterisation of the triazole CAG

Based on the estimated exposures, risk assessments of the cumulative exposures to the triazoles were performed for the 4 different scenarios following the proposed methodology (Chapter 1). As a tiered approach, HIs, adjusted HIs (adHI) and cumulative exposures based on RPF methodologies were successively determined deterministically. After this, probabilistic modelling of cumulated exposure according to the RPF methodology was performed as the final step of the tiered approach. Within the deterministic procedure, a further possible refinement, the use of processing factors, could have been applied at any step of the process, but this was only done in a few cases due to the lack of appropriate information.

See Table 26 below, which is identical in structure to table 1 from section 1.5, but filled with all possible combinations. Not all options were actually carried out. This will be discussed in Chapter 7.

Table 26. Overview of worked example of tiered cumulative risk assessment. Please note that the scheme has to be worked through for each of the identified exposure scenarios: actual_acute, actual_chronic, MRL-setting_acute and MRL-setting_chronic.

Hazard tiers		Exposure tiers			
		1	2	3	4
		Deterministic, MRL	Deterministic monitoring	Deterministic + processing	Probabilistic
A	ADI, ARfD	HI			
B	Adjusted* ADI, ARfD	adHI	adHI	adHI	
C	NOAEL*			RPF	
D	BMD*			RPF	RPF

* for common effect

4.1. Scenario 1: actual acute cumulative risk assessment

Risk assessment of the actual acute cumulative exposures based on the critical commodities (Section 3.6.1) was performed according to the following calculation methods:

Hazard Index (HI) - Tier A-2

First the HI of the combined background exposure is calculated as the sum of the HQ for acute effect – that is the ratios between the average chronic exposure and the regulatory ARfD - of the 7 compounds of the CAG corrected for the background contribution from the specific pesticide in the critical commodity. Then, a HQ reflecting the additional burden resulting from the consumption of a large portion of the pesticide/critical commodity combination at the highest residue level found in monitoring is added (high exposure event). This HQ is the ratio between the acute exposure calculated by PRIMo following the modified IESTI equation and the regulatory ARfD of the considered pesticide.

This calculation is repeated for each of the pesticides of the CAG.

$$HI_{acute} = \left(\frac{E_{\hat{\imath},LP,\hat{\jmath}}}{ARfD_{\hat{\jmath}}}\right) + \left(\sum_{j=1}^{n_j}\frac{E_j}{ARfD_j}\right) - \left(\frac{B_{\hat{\imath},\hat{\jmath}}}{ARfD_{\hat{\jmath}}}\right) = HQ_{\hat{\imath},LP,\hat{\jmath}} + \sum_{j=1}^{n_j}(HI_j) - HQ_{\hat{\imath},\hat{\jmath}}$$

HI_{acute} = Hazard Index for cumulative acute exposure

$E_{\hat{\imath},LP\hat{\jmath}}$ = Exposure to the specific pesticide $\hat{\jmath}$ from a LP size meal of the critical commodity $\hat{\imath}$

E_j = Combined background exposure to pesticide j from all commodities

$ARfD_{\hat{\jmath}}$ = Acute RV for the selected pesticide $\hat{\jmath}$

$ARfD_j$ = Acute RV for the pesticide j

$B_{\hat{\imath},\hat{\jmath}}$ = Background contribution from the selected pesticide $\hat{\jmath}$ in the critical commodity $\hat{\imath}$

$HQ_{\hat{\imath},LP,\hat{\jmath}}$ = Hazard Quotient for exposure to the specific pesticide $\hat{\jmath}$ from a LP size meal of the critical commodity $\hat{\imath}$

Hj_i = Hazard Index for the combined background exposure to pesticide j from all commodities.

$HQ_{\hat{\imath},\hat{\jmath}}$ = Hazard Quotient for the background exposure from the specific pesticide $\hat{\jmath}$ in the critical commodity $\hat{\imath}$

Adjusted Hazard Index (adHI) - (Tier B-2)

The principle of this calculation is essentially the same as for the calculation of the HI. The only difference is that an adjusted reference value based on the common effect (cranio-facial malformations) (*ARfDcom)* is used instead of the regulatory *ARfD*:

$$adHI_{acute} = \left(\frac{E_{\hat{\imath},LP,\hat{\jmath}}}{ARfD_{\hat{\jmath},com}}\right) + \left(\sum_{j=1}^{n_j}\frac{E_j}{ARfD_{j,com}}\right) - \left(\frac{B_{\hat{\imath},\hat{\jmath}}}{ARfD_{\hat{\jmath},com}}\right)$$

Relative Potency Factor-based methods (Tiers C-2 and D-2)

A cumulative background exposure expressed as equivalents of the index compound (IC) is first calculated by summing the average chronic exposures to each of the 7 pesticides in the CAG, adjusting their potencies to the IC with the relevant RPFs. Then the contribution from the consumption of a large portion of the pesticide/critical commodity combination (high exposure event), normalized to the potency of the IC is added, using again the relevant RPF. This exercise has been done using the 2 possible approaches for calculation of the RPFs (NOAEL and BMD5). The calculated cumulative RPF-adjusted exposure (ERPF,cum) is finally compared to and expressed as a percentage of the Acute Reference Dose (*ARfDic)* of the Index Compound (flusilazole), which is based on cranio-facial effects.

$$\frac{E_{RPF,cum}}{ARfD_{ic}} = \frac{\left(E_{\hat{\imath},LP,\hat{\jmath}} * RPF_{\hat{\jmath}}\right) + \left(\sum_{j=1}^{n_j}\left(E_j * RPF_j\right)\right) - \left(B_{\hat{\imath},\hat{\jmath}} * RPF_{\hat{\jmath}}\right)}{ARfD_{ic}}$$

RPF_j = Relative Potency Factor for pesticide j

$RPF_{\hat{\jmath}}$ = Relative Potency Factor for pesticide $\hat{\jmath}$

As discussed further in Section 6.3, risk assessments based on the adHI and NOAEL-based RPF approaches mathematically coincide when the same UFs are used to establish the adjusted toxicological reference values for all the pesticides of the CAG.

The results for Dutch consumers are summarised in table 27 and 28 below:

Table 27. Summary of risk assessments of dietary actual acute cumulative exposure of Dutch consumers (NL-total) by consumption of critical commodities

Residues	Critical commodity	Tier A-2	Tier B-2	Tier C-2	Tier D-2
		Hazard Index	Hazard Index adjusted	RPF-NOAEL	RPF-BMD
				% ARfD (flusilazole)	
Bitertanol	**Bananas**	0.781	0.026	2.69	3.28
Cyproconazole	**Table grapes**	0.143	0.022	2.21	1.19
Diniconazole	**Table grapes**	0.080	0.002	0.24	0.32
Epoxiconazole	**Leeks**	0.042	0.002	0.21	0.30
Flusilazole	**Table grapes**	0.523	0.006	0.59	0.58
Propiconazole	**Broccoli**	0.041	0.026	2.62	0.22
Triadimefon	**Pine apples**	0.275	0.042	4.21	5.02

Table 28. Summary of risk assessments of dietary actual acute cumulative exposure of Dutch children (NL-child) by consumption of critical commodities

Residues	Critical commodity	Tier A-2	Tier B-2	Tier C-2	Tier D-2
		Hazard Index	Hazard Index adjusted	RPF-NOAEL	RPF-BMD
				% ARfD (flusilazole)	
Bitertanol	**Bananas**	2.812	0.094	9.63	11.84
Cyproconazole	**Table grapes**	0.260	0.040	4.08	2.20
Diniconazole	**Table grapes**	0.143	0.005	0.44	0.62
Epoxiconazole	**Leeks**	0.083	0.004	0.43	0.65
Flusilazole	**Table grapes**	0.959	0.011	1.10	1.08
Propiconazole	**Broccoli**	0.063	0.038	3.86	0.36
Triadimefon	**Table grapes**	0.170	0.025	2.46	2.90

It is apparent from Tables 27 and 28 that under the assumptions made in this exercise, tier A-2, B-2, C-2 and D-2 result in HI and adHI below 1 and cumulative exposure below 100% of the ARfD of the IC. Therefore, had this been a real risk assessment, no further tiers would have been performed beyond tier A-2. The only exception is bitertanol in bananas for Dutch children, where in tier A2 the HI was above 1. For this scenario tier B-2 would have been needed to refine the risk assessment.

The rather high HI for this combination is due to a high intake (LP = 247g/day) of bananas combined with a high residue level (0.,52 mg/kg). However, at Tier B-2 the adHI is well below 1 for all combinations of pesticides/critical commodities including bitertanol/bananas. A similar outcome is found in the Tier C-2 and D-2 assessments based on the RPF-adjusted acute exposure, which for bitertanol/bananas is approximately 10% of the ARfD for the common effect of the IC. For all other pesticide/critical commodity combinations the RPF-adjusted exposures are at a lower level.

Note that this interpretation needs to be understood under the definition of background exposure used by the Panel in this exercise and that the comments made regarding exposure assessment under point 3.10 similarly apply to the deterministic risk assessment.

Probabilistic exposure modelling - tier C4/D4

Risk assessments at tier 4 are based on probabilistic exposure estimations (sec. 3.6) using either NOAEL derived RPFs (tier C4) or BMD derived RPFs (tier D4). The results are summarised in Tables 29 and 30. These two tables are generated from tables 12 and 13 by converting the exposure figures into percentage of the adjusted ARfD of flusilazole (Index compound; 0.5 mg/kg bw/day for common effect).

Table 29. Tier C-4 risk assessment of actual acute cumulative exposure of selected consumer groups. Exposures are estimated by probabilistic calculations based on NOAEL derived RPFs.

Consumer group	Age Rang years	Percentiles of estimated acute exposure at monitoring level % ARfD for flusilazole				
		95	99	99.9	99.99	Mean
Dutch total	**1 - 97**	<0.02	0.04	0.26	1.04	0.002
Dutch children	**1 - 6**	0.02	0.08	0.7	2.34	0.006

Table 30. Tier D-4 risk assessment of actual acute cumulative exposure of selected consumer groups. Exposures are estimated by probabilistic calculations based on BMD derived RPFs

Consumer group	Age Range years	Percentiles of estimated acute exposure at monitoring level % ARfD for flusilazole				
		95	99	99.9	99.99	Mean
Dutch total	**1 - 97**	<0.02	0.04	0.3	1.28	0.002
Dutch children	**1 - 6**	0.02	0.1	0.8	2.98	0.006

It is apparent from these tables that regardless of whether they are based on BMD or NOAEL derived RPFs, the actual acute cumulative exposure to the triazoles is (up to at least 99.99% of the distribution) estimated to be less than 3% of the ARfD.

It is highlighted that for scenario 1, two subscenarios were identified, (see Section 3.6).

1. routine evaluation of all available monitoring data, regarding acute risks for consumers ('total population').

2. enforcement situation; evaluation of individual samples ('consumers only').

The deterministic method addresses sub-scenario 2, whereas the probabilistic method addresses subscenario 1. However, as stated in 3.6, in principle the deterministic approach based on critical commodities could be used as a pragmatic first tier for sub-scenario 1, provided it results in an appropriate degree of conservatism.

The Rikilt Institute was not requested to probabilistically model consumer exposure in case of consumption of the critical pesticide/commodity combinations identified in the deterministic process (high expo-

sure events). Therefore, a comparison of tiers can only be performed for subscenario 1, assuming that the deterministic approach provides a pragmatic first tier for this scenario. By comparing Tables 27/28 and 29/30, it can be observed that the probabilistic estimated exposures (from 99 to 99.99 percentiles) account for a much lower percentage of the ARfD-value for the IC than does the intake from the critical commodity as calculated deterministically. It should be noted, when comparing the deterministic exposure estimations with the probabilistic estimations, that NDs were handled differently. The probabilistic estimations were made under the assumption that all NDs were 0 in contrast to the deterministic calculations, which were made assuming residues below LOR to be ½LOR in commodities with detection of residues above LOR in one or more samples (see Section 3.2.6). However, although the influence of assumptions on NDs in deterministic calculation may be large, in a sensitivity analysis concerning the probabilistic assessments, it was found that high percentiles (like 99.9th percentile) were not or less affected, because in this scenario exposures at high percentiles mainly are driven by samples containing high residue levels. Therefore, tentatively, the comparison can be made, although it must be kept in mind that there is an important conceptual difference between subscenarios 1 and 2 regarding the addressed populations of consumers.

It should be noted that the probabilistic estimated intakes are at such a low level that it is not necessary to assess the difference in risk assessments based on BMD derived RPFs and risk assessments based on NOAEL derived RPFs.

4.2. Scenario 2: actual chronic cumulative risk assessment

Risk characterisation of actual chronic cumulative exposures involves the same calculation tools as those mentioned under 4.1 (Scenario 1: actual acute cumulative risk characterisation). The only difference that is a major one, is that actual chronic risk results only from the background exposure and does not require any additional contribution from any particular pesticide/commodity combination at a particular extreme contamination level.

This changes the equations as follows:

Hazard Index (HI) – tier A2

The HI of the cumulative exposure (HI_{cum}) is calculated as the sum of the individual Hazard Quotients ($HQ_{i,j}$) for all the pesticides in the CAG:

$$HI_{cum} = \sum_{j=1}^{n_j}\left(\sum_{i=1}^{n_i} HQ_{i,j}\right) = \sum_{j=1}^{n_j} HI_j = \sum_{j=1}^{n_j}\left(\frac{E_j}{ADI_j}\right)$$

HQ_i = Hazard Quotient for exposure to a pesticide j in commodity i

HI_j = Hazard Index for exposure to pesticide j

E_j = Exposure to pesticide j from all commodities

ADI_j = RV for pesticide j

Adjusted Hazard Index (adHI) – tier B2:

The $adHI_{cum}$ is calculated using the same equations as for the *HI* but using the RV for common effect (ADI_{com}):

$$adHI_{cum} = \sum_{j=1}^{n_j}\left(\sum_{i=1}^{n_i} HQ_{i,j,com}\right) = \sum_{j=1}^{n_j} HI_{j,com} = \sum_{j=1}^{n_j}\left(\frac{E_j}{ADI_{j,com}}\right)$$

Relative Potency Factor-based methods – tier C2:

The long term cumulative exposure is equal to the background exposure, and expressed as equivalents of the IC. The calculation methodology has been described in Section 3.4. Note that only the NOAEL-based approach was used to derive the RPFs. The calculated cumulative RPF-adjusted exposure ($E_{RPF,cum}$) is finally compared to and expressed as a percentage of the chronic RV - ADI_{ic} - of the IC (cyproconazole), which is based on hepatotoxic effects.

$$\frac{E_{RPF,cum}}{ADI_{ic}} = \left(\frac{\sum_{j=1}^{n_j}\left(E_j * RPF_j\right)}{ADI_{ic}}\right)$$

E_j = Exposure to pesticide *j* from all commodities

RPF_j = Relative Potency Factor for pesticide *j*

As discussed further in section 6.3, risk assessments based on the adHI and NOAEL-based RPF approaches mathematically coincide when the same UFs are used to establish the adjusted toxicological reference values for all the pesticides of the CAG.

The results for the Dutch consumers are summarised in Table 31:

Table 31. Tier A-2, B-2 and C-2 risk assessments of actual chronic cumulative exposure of selected consumer groups. Deterministic exposure estimations are based on national monitoring data assuming that residue levels below LOR in samples of commodities with detectable residues are at ½LOR and at 0 in samples of commodities without any detectable residues.

Consumer group	Tier A-2	Tier B-2	Tier C-2	
	Hazard index	Hazard index adjusted	RPF-adjusted Actual Chronic exposure	
			µg cyproconazole eqv/kg bw/day	% ADI (cyproconazol)
Dutch total	0.10	0.034	0.68	3.4
Dutch children	0.24	0.071	1.41	7.0

It is apparent from the table that the HI (tier A-2) as well as the adjusted HI (tier B-2) for the cumulative exposure to the triazoles are well below 1.0 for all 4 consumer groups. It is noted that the HI is approximately 3 to 4 times higher than the adjusted Hazard Index.

Calculation of the HI and the adHI from the deterministic estimates of the exposures are the first tiers in the proposed methodology for risk assessment of cumulative dietary exposure to pesticides. They are considered as the most conservative tiers to assess the risk. Considering the obtained results, it should

not be necessary to proceed to higher tiers. However, in order to evaluate the methodology the next tiers were also addressed.

The next step (tier C-2) is assessment of the RPF-adjusted exposures compared to the ADI for common effect of the IC. For the triazoles, cyproconazole was identified as the IC for chronic exposure (see Chapter 2). However, it was only possible to draw up a set of RPF-factors based on NOAEL (Table 4), whereas BMD-data for the common chronic effect were not available, as explained in Section 2.3.2. The individual RPF-adjusted exposures for each of the triazoles are included in tables 8 and 9. The cumulative exposure is found by summing all the RPF-adjusted exposures to each of the individual triazoles. The final results are for the selected consumer groups are summarised in Table 31, which clearly shows that the RPF-adjusted cumulative exposure is below 10% of the ADI value of the IC for any of the consumer groups.

Probabilistic exposure modelling - tier C4

At tier C4, the risk assessments are based on probabilistic exposure estimations (see Section 3.7). For chronic effects, only NOAEL-based RPF factors were derived. The results are summarised in Table 32. This table is generated from Table 14 by converting the exposure figures into percentage of the adjusted ADI for the common effect of cyproconazole (Index Compound; 0.02 mg/kg bw/day).

Table 32. Tier C-4 risk characterisation based on probabilistic modelling of actual chronic cumulative exposure to triazole fungicides

Consumer group	Age Range years	Tier C-4				
		RPF-adjusted Actual Chronic exposure % ADI for cyproconazole				
		Percentiles of estimated chronic exposures				
		95	99	99.9	99.99	Mean
Dutch total	**1 - 97**	<0.5	0.5	0.5	0.5	0.09
Dutch children	**1 - 6**	0.5	1.0	1.5	1.5	0.22

The table clearly shows that the conclusion from this tier C-4 risk assessment of the chronic cumulative exposure to triazoles is the same as for the lower tiers and that the cumulative exposure is well below the adjusted ADI of the IC. It is noted that the probabilistic mean-values are lower than the tier 2 deterministic estimated RPF-adjusted values (see Table 31), which are based on average consumption data. This is in agreement with ranking of the tiers in the proposed methodology. However, the different handling of NDs should be considered when comparing the deterministic and probabilistic estimations (See footnote 20, page 90).

4.3. Scenario 3: acute cumulative risk assessment_MRL-setting

The deterministic calculation methods used under this scenario are quite similar to those described under 4.1. The only difference is that the highest residue levels found in monitoring for the critical commodities are substituted by the MRL level proposed for the pesticide/commodity combination under consideration. The same equations as described in Section 3.6.1 t were therefore used in this scenario for assessment of the cumulative exposures at MRL-level. The calculated HI, adHI and RPF-adjusted cumulative exposures for tier A1, B1 and C1/D1 are summarised for Dutch consumer groups in Tables 33 and 34 below[14].

[14] Risk assessment of the acute cumulative exposure of French consumers were not performed due to the lack of French data for LP-size meals and unit weights in the PRIMo model

Table 33. Summary of tier 1 risk assessments of acute cumulative exposures at MRL-level of Dutch (total) consumers

Residue	Commodity	Tier A-1	Tier B-1	Tier C-1		Tier D-1	
		Hazard index	Hazard index adjusted	RPF-adjusted acute exposure (NOAEL)		RPF-adjusted acute exposure (BMD)	
				µg flusilazole eq./kg bw/day	% ARfD (flusilazole)	µg flusilazole eq. /kg bw/day	% ARfD (flusilazole)
Bitertanol	Apple	3.53	0.12	60.1	12.0	74.1	14.8
	Banana	4.43	0.15	75.5	15.1	93.1	18.6
	Tomato	4.04	0.1	68.8	13.8	84.8	17.0
Cyproconazole	Table grapes	0.33	0.05	27.1	5.4	14.3	2.9
	Lettuce	0.04	0.01	2.4	0.5	1.4	0.3
	Peach	0.11	0.02	8.0	1.6	4.3	0.9
Diniconazole	Table Grapes	0.33	0.01	4.2	0.9	6.7	1.3
Epoxiconazole	Cabbage	0.24	0.01	5.7	1.1	10.3	2.1
	Wheat	0.04	0.002	0.9	0.2	1.3	0.3

Table 34 Summary of tier 1 risk assessments of acute cumulative exposures at MRL-level of Dutch children

Residue	Commodity	Tier A-1	Tier B-1	Tier C-1		Tier D-1	
		Hazard index	Hazard index adjusted	RPF-adjusted acute exposure (NOAEL)		RPF-adjusted acute exposure (BMD)	
				µg flusilazole eq./kg bw/day	% ARfD (flusilazole)	µg flusilazole eq. /kg bw/day	% ARfD (flusilazole)
Bitertanol	Apple	12.33	0.41	210.0	42.0	259.0	51.8
	Banana	16.08	0.54	273.7	54.7	337.8	67.6
	Tomato	9.48	0.32	161.5	32.3	199.2	39.8
Cyproconazole	Table grapes	0.61	0.10	49.7	9.9	26.3	5.3
	Lettuce	0.08	0.01	5.4	1.1	3.1	0.6
	Peach	0.29	0.05	23.0	4.6	12.4	2.5
Diniconazole	Table Grapes	0.61	0.02	7.8	1.6	12.4	2.5
Epoxiconazole	Cabbage	0.39	0.02	9.5	1.9	16.9	3.4
	Wheat	0.09	0.01	2.3	0.5	3.4	0.7

As for the chronic exposures at MRL level (Section 4.4), a tier A-1 risk assessment demonstrates that the HI is below 1 for the existing MRLs for cyproconazole, diniconazole and epoxiconazole in the selected commodities. The same conclusion can be drawn from the assessment of the adHI (tier B-1) and the RPF-adjusted exposures (tier C-1 and tier D-1). However, it is also clear from the table that the calculated HI for bitertanol exceeds the critical value for all 3 of the selected commodities for the Dutch

consumer groups[15]. Thus, a tier A-1 risk assessment of the existing MRL for bitertanol in the selected 3 commodities cannot provide sufficient reassurance for the possible risk from cumulative exposure to triazoles; an assessment at a higher tier is needed. However, it is also clear from the tables that the calculated adHI (Tier 1b) and the RPF-adjusted exposures (Tier C-1 and D-1) for bitertanol are below the critical values for all 3 commodities and for both Dutch consumer groups.

Note that this assessment is subject to the definition given in this exercise for 'background exposure' (see comments in Section 3.10) and that other possible approaches for this may be considered appropriate by risk managers.

It is noted for the evaluation of the methodology that the estimated RPF-adjusted exposures are higher for bitertanol, diniconazole and bitertanol when using RPFs based on BMDs as compared to exposures estimated by using RPFs based on NOAELs, while it is the opposite for cyproconazole.

Probabilistic exposure modelling - tier C4/D4

Risk assessments at tier C4 and D4 are based on probabilistic exposure estimations (sec. 3.6) using either NOAEL derived RPFs (tier C4) or BMD derived RPFs (tier D4). The results are summarised in the following Tables 35 and 36. These 2 tables are generated from tables 18 and 19 by converting the exposure figures into percentage of the ARfD of flusilazole (IC); ARfD for common effect is 0.5 mg/kg bw/day).

[15] For bitertanol, the exceedence of the HI is almost uniquely due to the pesticide/commodity combination under consideration therefore suggesting a potential exceedence of the regulatory ARfD of bitertanol for apples, bananas and tomatoes at MRL level. As mentioned in section 2.3 the PPR Panel for some active substances included in this exercise used data available from DARs which were not yet peer-reviewed. This was in particular the case for bitertanol for which the RMS proposed an ARfD based on chronic effects as a precautionary approach because it was considered that there were no clear NOAEL for developmental toxicity. This issue should be considered later at Risk Management level, on the basis of peer-reviewed ARfD.

Table 35. Tier C4 risk assessment of acute cumulative exposure of Dutch consumer groups for MRL setting of bitertanol in selected commodities. Percentiles and mean level of estimated acute cumulative exposure as % of ARfD for common effect of flusilazole. MRL data for a selected commodity-pesticide were used in combination with monitoring data of other combinations. Calculations were performed using NOAEL-derived RPFs, national food consumption data and residue data of all countries combined.

Commodity	Consumer group	Age range years	Percentiles of estimated acute exposure % ARfD for common effect of flusilazole				
			95	99	99.9	99.99	Mean
Bitertanol/Apple (2 mg/kg)	**Dutch total**	**1 - 97**	3.5	7.6	17.6	34.2	0.8
Bitertanol/Apple (2 mg/kg)	**Dutch children**	**1 - 6**	7.7	15.5	31.7	56.2	1.7
Bitertanol/Banana (3 mg/kg)	**Dutch total**	**1 - 97**	2.6	6.4	15.2	28.9	0.6
Bitertanol/Tomato (3 mg/kg)	**Dutch total**	**1 - 97**	5.2	13.5	3.3	51.4	1.2
Bitertanol/Tomato (3 mg/kg)	**Dutch children**	**1 - 6**	11.2	32.3	51.4	51.6	2.4
Cyproconazole/table grapes (0.2 mg/kg)	**Dutch children**	**1 – 6**	0.9	2.4	7.1	17.8	0.2
Cyproconazole/lettuce (0.05 mg/kg)	**Dutch children**	**1 – 6**	0.3	0.6	1.1	2.0	0.1
Cyproconazole/peach (0.2 mg/kg)	**Dutch children**	**1 – 6**	0.1	0.4	1.5	3.5	0.02
Epoxiconazole/cabbage (0.2 mg/kg)	**Dutch children**	**1 – 6**	0.3	0.7	1.7	3.4	0.08
Epoxiconazole/wheat (0.2 mg/kg)	**Dutch total**	**1 - 97**	0.2	0.2	0.5	1.1	0.06

Table 36. Tier D4 risk assessment of acute cumulative exposure of Dutch consumer groups for MRL setting of bitertanol in selected commodities. Percentiles and mean level of estimated acute cumulative exposure as % of ARfD for common effect of flusilazole. MRL data for a selected commodity-pesticide was used in combination with monitoring data of other combinations. Calculations were performed using BMD derived RPFs, national food consumption data and residue data of all countries combined.

Commodity	Consumer group	Age range years	Percentiles of estimated acute risk % ARfD for common effect of flusilazole				
			95	99	99.9	99.99	Mean
Bitertanol/Apple (2 mg/kg)	**Dutch total**	**1 - 97**	4.3	9.5	22.5	42.4	1.0
Bitertanol/Apple (2 mg/kg)	**Dutch children**	**1 - 6**	9.5	19.1	39.3	69.0	2.1
Bitertanol/Banana (3 mg/kg)	**Dutch total**	**1 - 97**	3.2	7.8	18.8	35.2	0.7
Bitertanol/Tomato (3 mg/kg)	**Dutch total**	**1 - 97**	6.5	16.6	40.6	63.5	1.5
Bitertanol/Tomato (3 mg/kg)	**Dutch children**	**1 - 6**	13.7	39.9	63.5	63.5	2.9
Cyproconazole/table grapes (0.2 mg/kg)	**Dutch children**	**1 - 6**	0.5	1.3	3.7	9.1	0.1
Cyproconazole/lettuce (0.05 mg/kg)	**Dutch children**	**1 - 6**	0.2	0.3	0.8	1.8	0.06
Cyproconazole/peach (0.2 mg/kg)	**Dutch children**	**1 - 6**	0.1	0.3	1.1	3.2	0.02
Epoxiconazole/cabbage (0.2 mg/kg)	**Dutch children**	**1 - 6**	0.6	1.4	3.1	5.9	0.2
Epoxiconazole/wheat (0.2 mg/kg)	**Dutch total**	**1 - 97**	0.3	0.4	0.7	1.5	0.1

The values obtained from exposure estimations based on NOAEL-derived RPFs are in this example of bitertanol and Dutch consumers lower than the values found by exposure estimations based on BMD-derived RPFs. It is pointed out in the Rikilt Institute report that the estimated exposure percentiles, independent of the RPFs applied, were on the same order of magnitude in the different countries. For example, the P99.9 of estimated exposure for adults using BMD-derived RPFs were 90.4, 90.6 and 59.1 µg equivalents of flusilazole/kg bw/d in France, Italy and The Netherlands, respectively. The results obtained with NOAEL-derived RPFs show a similar picture. Estimated exposure levels calculated by using RPFs derived from NOAELs are usually lower compared to the same calculations based on RPFs derived from BMDs for MRL settings for bitertanol. The RPF factor for bitertanol is 1.7 and 2.1, when based on NOAELs and BMDs, respectively. A lower RPF factor for the major contributor bitertanol resulted in a lower estimated exposure level. The opposite is found in scenarios in which a MRL is set for cyproconazole. The 99.9 percentile estimated exposure level for Dutch children is estimated to be 7.4 and 5.7 µg equivalents of flusilazole/kg bw/d using RPFs derived from NOAELs and BMDs, respectively. Again this correlates with the size of the RPFs which are 4.2 when derived from NOAELs and 2.2 when derived from BMDs.

4.4. Scenario 4: chronic cumulative risk assessment_MRL-setting

The first 3 tiers in the risk assessment of the chronic cumulative exposures in the MRL-setting scenario were performed by deterministic calculations of the exposures followed by calculation of the HIs, the adHIs and the adjusted exposures through the NOAEL-based RPF methodology.

Essentially, the calculations consist of adding to the background chronic risk (which is equal to the actual cumulated chronic risk characterised under 4.2) a contribution resulting from the exposure to the pesticide/commodity of interest at the STMR level. This gives:

Hazard Index (HI) – tier A1:

$$HI_{cum} = HQ_{\tilde{\imath},\hat{\jmath},STMR} + \left(\sum_{j=1}^{n_j} HI_j\right) - HQ_{\tilde{\imath},\hat{\jmath}} = \left(\frac{E_{\tilde{\imath},\hat{\jmath},STMR}}{ADI_{\hat{\jmath}}}\right) + \left(\sum_{j=1}^{n_j} \frac{E_j}{ADI_j}\right) - \left(\frac{B_{\tilde{\imath},\hat{\jmath}}}{ADI_{\hat{\jmath}}}\right)$$

$HQ_{\tilde{\imath},\hat{\jmath},STMR}$ = Hazard Quotient for the exposure to the specific pesticide $\hat{\jmath}$ at STMR-level in commodity $\tilde{\imath}$

HI_j = Hazard Index for the background exposure from all commodities to the pesticide j

$HQ\tilde{\imath},\hat{\jmath}$ = Hazard Quotient for background exposure from the specific pesticide $\hat{\jmath}$ at monitoring level in commodity $\tilde{\imath}$.

$E_{\tilde{\imath},\hat{\jmath},STMR}$ = Exposure to the pesticide $\hat{\jmath}$ at STMR-level in commodity $\tilde{\imath}$

E_j = Background exposure from all commodities to a pesticide j at monitoring level

$B_{\tilde{\imath},\hat{\jmath}}$ = Background exposure to the specific pesticide $\hat{\jmath}$ at monitoring level in commodity $\tilde{\imath}$

ADI_j = Toxicological reference value for pesticide j

$ADI_{\hat{\jmath}}$ = Toxicological reference value for pesticide $\hat{\jmath}$

Adjusted Hazard Index (adHI) – tier B1:

The *adHI* is calculated using the same equations as for the *HI* but using the reference value for common effect (ADI_{com}):

$$adHI_{cum} = \left(\frac{E_{\tilde{\imath},\hat{\jmath},STMR}}{ADI_{\hat{\jmath},com}}\right) + \left(\sum_{j=1}^{n_j} \frac{E_j}{ADI_{j,com}}\right) - \left(\frac{B_{\tilde{\imath},\hat{\jmath}}}{ADI_{\hat{\jmath},com}}\right)$$

Relative Potency Factor-based methods:

In this scenario, the long term exposure is calculated as the sum of the RPF adjusted exposure caused by the pesticide/commodity at STMR-level and the average chronic background exposures expressed as equivalents of the IC. Only the NOAEL approach was used in this scenario for deriving the RPFs. The calculated cumulative RPF-adjusted exposure ($E_{RPF,cum}$) is finally compared to and expressed as a percentage of the chronic reference value - ADI_{ic} - of the IC(cyproconazole).

$$\frac{E_{RPF,cum}}{ADI_{ic}} = \left(\frac{E_{\tilde{\imath},\hat{\jmath},STMR} * RPF_{\hat{\jmath}} + \left(\sum_{j=1}^{n_j} \left(E_j * RPF_j \right) \right) - B_{\tilde{\imath},\hat{\jmath}} * RPF_{\hat{\jmath}}}{ADI_{ic}} \right)$$

RPF_j = Relative Potency Factor for pesticide j

$RPF_{\hat{\jmath}}$ = Relative Potency Factor for pesticide $\hat{\jmath}$

$E_{\tilde{\imath}\hat{\jmath},STMR}$ = Exposure to the pesticide $\hat{\jmath}$ at STMR-level in commodity $\tilde{\imath}$

$B_{\tilde{\imath}\hat{\jmath}}$ = Background exposure to the specific pesticide $\hat{\jmath}$ at monitoring level in commodity $\tilde{\imath}$

As discussed further in section 6.3, risk assessments based on the adHI and NOAEL-based RPF approaches mathematically coincide when the same UFs are used to establish the adjusted toxicological reference values for all the pesticides of the CAG.

The results for Dutch consumer groups are summarised in Tables 37 and 38.

Table 37. Risk characterisation in the MRL-setting scenario (using STMR-values) for selected pesticide/commodity combinations based on deterministic estimations of the cumulative chronic exposure of the Dutch general population.

Residue	Commodity	Tier A-1	Tier B-1	Tier C-1	
				RPF-adjusted exposures (NOAEL)	
		Hazard index	Hazard index adjusted	µg cyproconazole eq./kg bw/day	% ADI for liver effect (cyproconazole)
Bitertanol	Apple	0.28	0.05	1.03	5.1
	Banana	0.16	0.04	0.78	3.9
	Tomato	0.43	0.07	1.32	6.6
Epoxiconazole	Wheat	0.14	0.05	0.93	4.7

Table 38. Risk characterisation in the MRL-setting scenario (using STMR-values) for selected pesticide/commodity combinations based on deterministic estimations of the cumulative chronic exposure of Dutch children.

Residue	Commodity	Tier A-1	Tier B-1	Tier C-1	
				RPF-adjusted exposures (NOAEL)	
		Hazard index	Hazard index adjusted	µg cyproconazole eq./kg bw/day	% ADI for liver effects (cyproconazole)
Bitertanol	Apple	1.19	0.17	3.30	16.5
	Banana	0.53	0.10	1.98	9.9
	Tomato	0.72	0.12	2.35	11.8
Epoxiconazole	Wheat	0.32	0.10	2.00	10.0

The HI for cumulative exposure of Dutch children to bitertanol on apples is greater than 1.0. However, the adHI is 0.17. Furthermore, for the Dutch consumer groups, the RPF-adjusted exposures are for all combinations of bitertanol and the selected commodities below 20% of the ADI value of the IC.

Probabilistic exposure modelling - tier C4

At tier C4, the risk characterisations are based on probabilistic exposure estimates. These were performed using the NOAEL-based RPF approach. The results are summarised in Table 39. This table is generated from Table 23 by converting the exposure scores into percentages of the adjusted ADI for the common effect of cyproconazole (IC; 0.02 mg/kg bw).

Table 39. Tier C-4 risk characterisation based on probabilistic modelling of chronic cumulative exposure to triazole fungicides in the MRL-setting scenario using Field Trial data of selected pesticide/commodity combinations.

Commodity	Consumer group	Age range	Estimated chronic combined risk % ADI for cyproconazole for common effect (hepatotoxicity)					
			90	95	99	99.9	99.99	Mean
Bitertanol/Apple	**Dutch total**	**1 - 97**	4.5	6	10.5	17.0	18.5	1.5
Bitertanol/Apple	**Dutch children**	**1 - 6**	18.5	23.5	35.0	42.5	43.5	7.5
Bitertanol/Banana	**Dutch total**	**1 - 97**	1	1.5	4.0	6.5	7.0	0.5
Bitertanol/Tomato	**Dutch total**	**1 - 97**	7.5	9.5	15.5	22.0	23.5	3.5
Bitertanol/Tomato	**Dutch children**	**1 - 6**	12.5	16.5	26.0	32.5	33.0	5.5
Epoxiconazole/wheat	**Dutch total**	**1 - 97**	2.0	2.0	3.0	4.0	4.0	1.0
Epoxiconazole/wheat	**Dutch children**	**1 - 6**	3.5	4	5.5	6.0	6.5	2.5

Once again, the consumption of apples by Dutch children is causing the most remarkable result but still at percentile 99.99 well below the adjusted ADI of the IC.

5. Uncertainties affecting the assessments (quantified and unquantified).

As discussed in the general opinion on cumulative risk assessment (EFSA, 2008a), all risk assessments are subject to uncertainty. Because cumulative assessments consider exposure and toxicity for multiple pesticides, they are affected by more potential sources of uncertainty than assessments of individual pesticides. It is important to characterize the degree of uncertainty associated with risk estimates, so that it can be taken into account in risk management (Madelin, 2004; Codex, 2007).

EFSA previously stated that it would be efficient to use a tiered approach to analyzing uncertainties (EFSA, 2006a). Each individual source of uncertainty may be analyzed at one of three levels: qualitative, deterministic or probabilistic. Note that it is not necessary to treat all uncertainties in an assessment at the same level; on the contrary, it is likely to be more efficient to quantify only the most substantial uncertainties. Initially, all significant uncertainties may be analyzed qualitatively. This may be sufficient, if the outcome is clear enough for risk managers to reach a decision. Otherwise, those uncertainties that appear critical to the outcome may be analyzed deterministically or probabilistically. A way to quantify uncertainties is to perform sensitivity analyses, where the values selected for a variety of input parameters or datasets are varied and the degree to which this influences the risk estimates is evaluated.

What type of uncertainty analysis was performed in each of the tiers of the risk assessment is described below.

5.1. Sensitivity analyses

Assigning residue levels to samples with residue levels below LOR

When performing exposure assessments for pesticides, samples with residue levels below the LOR are commonly assumed to contain no residue. However, a certain fraction of the commodities will have been treated with the pesticide, and hence some of these so-called NDs will actually contain the pesticide, albeit at levels lower than the LOR. (see Section 3.2.6).

In this section, the impact of several alternative assumptions for handling NDs was investigated, both for the deterministic and the probabilistic assessments. For the deterministic assessments, five different calculations of background exposures (actual chronic exposure) were made using the monitoring data supplied by the Rikilt Institute. The calculations were made for five different scenarios for handling the ND values and using consumption data for Dutch children, which were considered to be the most sensitive consumer group:

- **I:** Residue levels in all samples without detectable residues were set at 0
- **II:** Residue levels in samples with residues below LOR were set at ½LOR for commodities that contained at least one detectable residue of the pesticide of interest but at zero for commodities that had no detectable residues
- **III:** Residue levels in samples with residues below LOR were set at the LOR for commodities with at least one detectable residue but at zero for commodities without any detectable residues
- **IV:** Residue levels in all samples without detectable residues were set at ½LOR
- **V:** Residue levels in all samples without detectable residues were set at (the full) LOR

The impact of these assumptions on the outcome of the assessments for Dutch children is displayed in Tables 40 through to 43 for various acute and chronic deterministic scenarios under both the NOAEL-estimated RPF and BMD-estimated RPF situations. The results show that assumptions regarding concentration values associated with NDs can have substantial influence on the estimated exposures. For example, a factor of up to 5000 between the low and high exposure estimates was found for single compounds among the five different scenarios. This results in an impact on the cumulative risk assessment by a factor of up to 300. The PPR Panel considered background exposures calculated according to scenario II in which residue levels in samples with residues below LOR were assumed to be present at ½LOR for commodities with findings but at zero for commodities without detectable residues to be the most reasonable and practicable approach to use in the deterministic assessments performed in this exercise (see Section 3.2.7); specifically, Scenario II represents a situation between Scenario I in which residue levels in all samples without detectable residues were set to zero (likely to be an underestimate), and Scenarios III, IV, and V in which residue levels were set to various levels up to the full LOR. However, the various methods of handling NDs should be investigated further and any preference for one handling method over another cannot at this time be generalized. A variety of methods for handling NDs using various statistical and other tools could be based on an evaluation of the distribution of the measured residue values together with information on registered uses, knowledge of the plant and soil metabolism, and data on the percentage of treated crops.

Table 40. Chronic background exposures to each active substance estimated for different residue levels in samples without detectable residues in Dutch children. Background exposures include all 11 triazoles when assessing chronic cumulative exposure, whereas only 7 (marked with an asterisk) are included when assessing acute cumulative exposure. (note that column II can also be found in section 3.4, table 9)

Residues	Chronic background exposures (µg/kg bw/day)				
	I	II	III	IV	V
Bitertanol*	0.0093	0.1084	0.2077	0.8116	1.6141
Cyproconazole*	0.0004	0.0456	0.0906	0.8034	1.6066
Difenoconazole	0.0065	0.3113	0.6160	0.8050	1.6034
Diniconazole*	0.0005	0.0375	0.0745	0.8035	1.6065
Epoxiconazole*	0.0003	0.0358	0.0712	0.8034	1.6642
Flusilazole*	0.0008	0.0362	0.0716	0.8035	1.6062
Myclobutanil	0.0234	0.2379	0.4524	0.8229	1.8564
Propiconazole*	0.0013	0.0799	0.1588	0.8046	1.6074
Tebuconazole	0.0240	0.3488	0.7504	0.8304	1.7136
Triadimefon*	0.0304	0.2240	0.4176	0.8288	1.6304
Triadimenol	0.0715	0.3785	0.6860	0.8610	1.6510

I: Residue levels in all samples without detectable residues at 0
II: Residue levels in samples with residues below LOR at ½LOR for commodities with findings but at 0 for commodities without findings
III: Residue levels in samples with residues below LOR at LOR for commodities with findings but at 0 for commodities without findings
IV: Residue levels in all samples without detectable residues at ½LOR
V: Residue levels in all samples without detectable residues at LOR

Table 41. Sensitivity analysis for use of censored data for deterministic estimation of actual chronic exposure in Dutch children. (note that column II, row %ADI can be compared to Section 4.2, Table 30)

Residues	RPF (NOAEL) chronic	RPF (NOAEL) adjusted chronic exposures (µg cyproconazole eq./kg bw/day)				
	IC (cyprocona-zole)	I	II	III	IV	V
Bitertanol	**2**	0.0186	0.22	0.42	1.62	3.23
Cyproconazole	**1**	0.0004	0.05	0.09	0.80	1.61
Difenoconazole	**2**	0.0130	0.62	1.23	1.61	3.21
Diniconazole	**0.4**	0.0002	0.02	0.03	0.32	0.64
Epoxiconazole	**2.5**	0.0008	0.09	0.18	2.01	4.16
Flusilazole	**4**	0.0030	0.14	0.29	3.21	6.42
Myclobutanil	**0.05**	0.0012	0.01	0.02	0.04	0.09
Propiconazole	**0.6**	0.0008	0.05	0.10	0.48	0.96
Tebuconazole	**0.1**	0.0024	0.03	0.08	0.08	0.17
Triadimefon	**0.1**	0.0030	0.02	0.04	0.08	0.16
Triadimenol	**0.4**	0.0286	0.15	0.27	0.34	0.66
Cumulative	**-**	0.072	1.40	2.74	10.61	21.32
%ADI (cyproconazole) for common effect (=20 µg/kg bw/day)	**-**	**0.36**	**7.01**	**13.71**	**53.07**	**106.61**

I: Residue levels in all samples without detectable residues at 0
II: Residue levels in samples with residues below LOR at ½LOR for commodities with findings but at 0 for commodities without findings
III: Residue levels in samples with residues below LOR at LOR for commodities with findings but at 0 for commodities without findings
IV: Residue levels in all samples without detectable residues at ½LOR
V: Residue levels in all samples without detectable residues at LOR

Table 42. Sensitivity analysis for use of censored data for deterministic estimations of actual acute exposure in Dutch children. Adjusted exposures based on NOAEL-RPFs

Residues	RPF (NOAEL) acute	RPF (NOAEL) adjusted acute exposures (µg flusilazole eq./kg bw/day)				
	IC (fluzila-zole)	I	II	III	IV	V
Bitertanol	**1.7**	0.0158	0,18	0,35	1,38	2,74
Cyproconazole	**4.2**	0.0017	0,19	0,38	3,37	6,75
Diniconazole	**0.6**	0.0003	0,02	0,04	0,48	0,96
Epoxiconazole	**0.8**	0.0003	0,03	0,06	0,64	1,33
Flusilazole	**1**	0.0008	0,04	0,07	0,80	1,61
Propiconazole	**1.7**	0.0022	0,14	0,27	1,37	2,73
Triadimefon	**1**	0.0304	0,22	0,42	0,83	1,63
Cumulative	**-**	0.051	0,82	1,59	8,88	17,76
%ARfD (flusilazole) for common effect (=500 µg/kg bw/day)	**-**	**0.010**	**0,17**	**0,32**	**1,78**	**3,55**

I: Residue levels in all samples without detectable residues at 0
II: Residue levels in samples with residues below LOR at ½LOR for commodities with findings but at 0 for commodities without findings
III: Residue levels in samples with residues below LOR at LOR for commodities with findings but at 0 for commodities without findings
IV: Residue levels in all samples without detectable residues at ½LOR
V: Residue levels in all samples without detectable residues at LOR

Table 43. Sensitivity analysis for use of censored data for deterministic estimations of actual acute exposure in Dutch children. Adjusted exposures based on BMD-RPFs

Residues	RPF (from BMD)	RPF (from BMD) adjusted acute exposures (µg flusilazole eq./kg bw/day)				
	IC (fluzila-zole)	I	II	III	IV	V
Bitertanol	**2.1**	0.0195	0.23	0.44	1.70	3.39
Cyproconazole	**2.2**	0.0009	0.10	0.20	1.77	3.53
Diniconazole	**1**	0.0005	0.04	0.07	0.80	1.61
Epoxiconazole	**1.5**	0.0005	0.05	0.11	1.21	2.50
Flusilazole	**1**	0.0008	0.04	0.07	0.80	1.61
Propiconazole	**0.1**	0.0001	0.01	0.02	0.08	0.16
Triadimefon	**1.2**	0.0365	0.27	0.50	0.99	1.96
Cumulative	**-**	0.06	0.73	1.41	7.36	14.75
%ARfD (flusilazole) for common effect (=500 µg/kg bw/day)	**-**	**0.012**	**0.15**	**0.28**	**1.47**	**2.95**

I: Residue levels in all samples without detectable residues at 0
II: Residue levels in samples with residues below LOR at ½LOR for commodities with findings but at 0 for commodities without findings
III: Residue levels in samples with residues below LOR at LOR for commodities with findings but at 0 for commodities without findings
IV: Residue levels in all samples without detectable residues at ½LOR
V: Residue levels in all samples without detectable residues at LOR

In the Rikilt Institute assignment (van Klaveren et al., 2009), a zero level was assigned to ND samples analyzed in monitoring programmes. ND samples from field trial data however were assigned LOR, because in these trials 100% of the crop is treated. To demonstrate the effect on the estimated exposure of assigning levels to ND samples, additional actual acute exposure calculations were performed using BMD-derived RPFs in which ND wheat samples for epoxiconazole were set at ½ LOR (= ½ x 0.05 mg/kg) in order to simulate three scenarios of percentage crop treated, namely 10%, 50% and 100% (which represents the worst case situation). In these calculations all other ND RAC –pesticide combinations were assumed to contain no residue (see Figure 8 in van Klaveren et al., 2009 for the results). Assigning ½ LOR to ND wheat samples analyzed for epoxiconazole resulted in a slight increase in estimated exposure over all percentiles of estimated exposure with increasing level of percentage crop treated. The relative increase was highest at the lower percentiles of estimated exposure (≤ P95).

As demonstrated by Boon et al. (2003), the effect of replacing NDs with LOR on the estimated exposure percentiles depends on the percentage of NDs in the whole database, and the LOR level relative to the levels present in the monitoring database. For acute exposures, it was found that generally intermediate percentiles (e.g. P95) were influenced most, whereas high percentiles (like P99.9) were not or affected to a lesser extent (Boon et al., 2003). The percentage of crop treated will also affect the results. The results plotted in Figure 8 in van Klaveren et al. (2009) accord with these results. Very likely the replacement of some of the NDs with low levels of one pesticide (epoxiconazole) does not influence the upper

part of the estimated exposure distribution, because this part is dominated by samples with high cumulative levels. The influence of levels assigned to NDs was, however, not tested for other RACs and might be more significant for RAC –pesticide combinations with a possible higher contribution to the estimated exposure levels.

The uncertainty due to NDs was not examined by sensitivity analysis for the probabilistic chronic assessments, but its influence there can be expected to be greater than in acute assessments, as low residues will have more influence on average exposure than on peak exposures.

In addition to assumptions on handling NDs, the Rikilt Institute report (van Klaveren et al., 2009) also addresses other sources of uncertainty influencing the outcome of the probabilistic calculations, like model uncertainties and uncertainty related to the completeness in residue and/or consumption data (bootstrap method). Furthermore, a database was generated in which all national residue concentration data were combined. This database was used to reduce uncertainties in the estimated exposure results related to the completeness of the monitoring and differences in monitoring practices in countries, as recognized in the EFSA opinion on acute dietary intake (EFSA, 2007b).

5.2. Evaluation of unquantified uncertainties

In the Panel's previous opinion on cumulative risk assessment (EFSA, 2008a) a table was presented with a qualitative evaluation of the influence of uncertainties on cumulative risk assessment when consuming commodities containing two or more CAG compounds. In this Chapter, the table is copied, and amended with a third column indicating the direction and magnitude of uncertainties specified for the worked example on triazoles.

Table 44. Qualitative evaluation of influence of uncertainties on cumulative risk assessment when consuming commodities containing two or more CAG compounds. Key to direction and magnitude: +, ++, +++ = uncertainty with potential to cause small, medium or large over-estimation of risk (i.e.: over-estimation of the ratio of exposure for high consumers to levels that might cause harm, hence increased conservativism); -, --, --- = uncertainty with potential to cause small, medium or large under-estimation of risk (i.e.: under-estimation of the ratio of exposure for high consumers to levels that might cause harm, hence reduced conservativism). The relative importance of these and also of other uncertainties not listed here may vary from one cumulative assessment to the next, and should be considered case by case.

Source of uncertainty/variability	Direction and magnitude, as expected in general opinion	Direction and magnitude, specific for triazole exercise
Toxicology		
Criteria for defining CAG		-/++
Judgement on inclusion of individual compounds in CAG		+/++ (acute) --/++ (chronic)
Use of NOAEL from standard toxicity studies as a Reference Point - might either over- or underestimate the true NOAEL, depending on dose spacing and on the sensitivity of the toxicological end-point that is assessed.	- -/++	-/++
Use of BMD to give an estimate of potency,	-/+	- /+
Intraspecies UF (default 10)		- / +++
Interspecies UF (default 10)		- / +++
Quality and adequacy of toxicity data, appropriate experimental design		-/+
Time-course of effects may differ between compounds. Since acute exposure is assessed as 24-hours exposure, for compounds showing effects that are reversible in a few hours such an assessment would overestimate the effects. Alternatively there could be carry-over from consumption on a previous day	-/+++ (for acute exposure)	+/++
All of the methods assume that compounds have parallel dose-response curves, which is not necessarily true. It is not possible to determine a priori whether this will result in more or less conservatism in the assessment, this will vary on a case-by-case basis. A further complication is that whilst the dose-response curves may be non-parallel in the range of observable responses, it is not possible to determine how the curves relate to each other at lower levels of exposure	-/+	-/+
Refinement of grouping can reach different levels of precision, depending on available data and needs. According to the step-wise approach described, "unrefined" CAGs will include more compounds than refined CAGs. Therefore, the lower tiers of refinement lead to an overestimation of expected toxicological effects.	+/+++ (for lower tier assessments)	+ (acute) +/++ (chronic)
Residues		
Monitoring programmes do not cover all relevant commodities	-/- - - (if no attempt is made to extrapolate from monitored commodities)	- chronic -/-- acute
Sampling uncertainty due to limited monitoring data. This uncertainty will be large in many cases, where the number of samples (especially positive samples) is small.	- - -/+++	- - -/+++
Sampling uncertainty due to limited number of units per composite sample	- - /+ +	- - /+ +

Measurement uncertainties in pesticide concentrations	-/+	-/+
Handling of data below the LOD, LOQ or LOR	- - -/+++	+ deterministic - probabilistic
Extrapolation to unmonitored commodities	-/+	-/+
Lack of monitoring data for new compounds		-/--
Residue data from monitoring samples may overestimate the real exposure of the consumer, due to the fact that sampling can be done at several points in the distribution chain (e.g. farm gate, retailer, supermarket) and that at the time of consumption the residue may have declined	+/+++ (only for actual exposure scenarios)	+/+++ (only for actual exposure scenarios)
Monitoring programmes never include all pesticides present in the worldwide market. Therefore not all compounds in the CAG may be included in the exposure assessment	-/- --	--
Data on the effect of processing (e.g. peeling, canning, cooking) on residues are rather limited, incomplete and frequently based on a limited number of measurements. Most frequently they will/can not be used.	+/+++	++
Concentrations in edible and non-edible parts of commodities may differ, and could cause over- or underestimation of intakes if the non-edible parts were included in the residue analysis.	- /++	+
Relation of supervised trial data to residues in the marketplace	+/+++ (only for actual exposure scenarios, early tier assessment)	+ (used for probabilistic calculations in scenarios 3 and 4)
Omission of potential contribution of residues from preceding rotational crops	- (only relevant when supervised trial data are used)	n.a.
Omission of potential contribution of residues in animal products	-	n.a.
Selection of commodities for monitoring is sometimes targeted on those thought likely to contain high residues. This will tend to overestimate the general distribution of residues.	+/+++	+/+++
Use of residue as defined for MRL/enforcement to represent all residues of toxicological concern	- - -/+	-
Using a conversion factor to correct residues as defined for MRL/enforcement to represent all residues of toxicological concern	-/+	n.a.
Treatment of unit-to-unit variation (e.g. choice of variability factor) in acute assessments. Probabilistic assessments used average variability factors, deterministic assessments used higher, standard values.	- -/++	+/++ deterministic -/+ probabilistic
Future change of pesticide usage/residue levels. Change in % crop treated could significantly increase or decrease chronic exposures for large sections of the population, and could increase the frequency of peak acute exposures.	- - -/+++ (for chronic exposure)	- - -/+++ (for chronic exposure)
Field trial data will tend to overestimate concentrations in treated produce, because field trial conditions are supposed to tend towards a worst case (e.g. maximum number and rate of applications, minimum intervals between and after treatment). This will tend to overestimate intakes, although due to the limited number of trials per commodity (4 or 8) the opposite (underestimation of residues and hence intakes) may also occur.	- / ++ (only for scenarios using field trial data)	
Consumption data		
Influence of survey design (method used, season, days of week, etc)	- --/++	-/+
Use of old food consumption survey data may not reflect recent increases (or decreases) in consumption of fruit and vegetables.	- - /++	- (specific for Dutch consumers used in the current worked example)
Statistical uncertainty due to limited number of persons surveyed (especially for rarely-consumed commodities)	- /+	-/+

Measurement/reporting uncertainty in consumption surveys.	-/+	-/+
Model uncertainties regarding extrapolation from short-term surveys to long-term average consumption	-/+	-/+
Ambiguity in food coding descriptions	-/+	-/+
Extrapolation from food as eaten to commodities: the recipes used for this may include both underestimates and overestimates in different cases.	- -/++	- /+
Extrapolation of consumption data from one country to another		-- / ++
Uncertainty in estimation of food weights	-/+	-/+
Estimation of large portion size, e.g. 97.5th percentile (when used)	- -/+ (for first tier exposure assess-ment)	- -/+ (for first tier exposure as-sessment)
Relation of consumption to body weight	+	+
Differences between probabilistic models	-/+	-/+
IOM method: likely to underestimate % consumers but overestimate upper tail of chronic exposure distribution. However, could underes-timate upper tail if survey is too small to detect individuals with un-usual habitual combinations of commodities.		-/++
PRIMo database (deterministic assessments): represents average in-takes (including non-consumers). Could lead to substantially underes-timating potential for exceedance of ADI.		- - / - - -

5.3. Overall assessment of quantified and unquantified uncertainties

The PPR Panel noted in the previous opinion that sources of uncertainty rated +++ or - - - in the qualitative evaluation warrant sensitivity analysis and provide the greatest scope for refinement of the assessment.

In a definitive risk assessment it would be essential for the risk assessor to review the uncertainties identified in the table and arrive at a conclusion regarding the overall level of uncertainty. This should be expressed in terms of the overall influence of the uncertainties on the final outcome of the assessment (e.g. can it be considered to be conservative or unconservative overall). Since the current exercise is not a definitive assessment, such an overall evaluation has not been undertaken. However, the table above is presented as an indication of the uncertainties that will need to be considered in future assessments.

6. Evaluation of the methodology

As emphasised in the introduction to this opinion, the present exercise is not to be taken as the final EU risk assessment of cumulative dietary intake of triazoles. The aim is primarily to use it as a worked example for testing as many tiers of the approach as possible. Based on the experience from this exercise, advantages and disadvantages of the proposed methodology to assess cumulative effects from dietary exposure through food from pesticides on human health are described and discussed in the following sections. These focus on the 3 main topics of the tiered approach, that is hazard characterisation, exposure estimation and risk characterisation.

6.1. Hazard characterisation

6.1.1. Identification of the Cumulative Assessment Group (CAG)

The first step in the hazard characterization is the identification of the CAG. Initial considerations were given to chemical structure, pesticidal mechanism and toxicological effects. The triazoles are one of the largest pesticide groups, comprising 26 compounds used as pesticide active substances. The common structural moiety is the presence of a triazole ring. In addition, the target effect for the pesticidal activity of all triazoles is the inhibition of C14-demethylase in sterol biosynthesis (erg11/cyp51) in fungi. This mechanism of pesticidal action has human relevance, as CYP51-catalysed sterol 14-demethylase is not only expressed in fungi but is also found in many other species including mice, rats and humans. Many triazoles cause specific developmental effects, which may be an acute effect. Cranio-facial malformations were selected as the common endpoint for this exercise. However, it should be noted that some other developmental effects, such as renal variations / malformations, could have been considered a common effect and in a definitive assessment, all possible common effects would have to be considered rigorously and evaluated if necessary.

The triazoles cause effects in the liver, on repeated exposure. For the purpose of this exercise, this was considered a chronic effect. The CAG comprised the seven compounds in the acute CAG and four additional compounds for which there were extensive monitoring data. This was done for pragmatic reasons to obtain a CAG of manageable size for the purpose of this exercise. Although effects of some triazoles were observed on reproduction, more compounds were hepatotoxic, and the NOAELs for this effect were similar to or lower than those for reproductive or systemic toxicity in multigeneration studies for 8 of the 11 triazoles in this CAG (see Appendix B). Such considerations can be used in determining whether assessment for additional common effects will be necessary. With respect to human relevance, triazoles were considered appropriate for CRA because they are frequently detected in monitoring programmes.

The compounds were further evaluated to identify a possible common mode/mechanism of toxicity and associated endpoints. This was done by considering the information provided in the DARs prepared by Rapporteur Member States. If no DAR was available other sources of information included JMPR and US EPA evaluations and published scientific articles. In several cases the DARs used as a source of information were not peer-reviewed by EFSA at the time they were consulted (see Appendix C). It was not possible to refine the CAGs further on the basis of the information available. Nevertheless, this can be an important step in the tiered approach, as only those compounds acting on the same or related molecular targets should be included in a CAG. However, in the absence of evidence to the contrary the methodology proposed by the Panel requires that compounds be retained in the CAG. This is an exclusion approach, where compounds possessing the basic characteristics of the CAG are excluded only if it can be shown that they do not exhibit the common mechanism, if known. The alternative, for example as used by the US EPA, is an inclusion approach, where compounds have to meet specific mechanistic criteria before inclusion in the CAG.

For risk assessment of short-term (acute) intake, the weight of evidence supported grouping seven triazoles (bitertanol, cyproconazole, diniconazole, epoxiconazole, flusilazole, propiconazole and triadime-

fon) because they caused a common developmental effect (cranio-facial malformation) possibly via a common mode/mechanism of action.

For chronic assessment eleven triazoles (bitertanol, cyproconazole, difenoconazole, diniconazole, epoxiconazole, flusilazole, myclobutanil, propiconazole, tebuconazole, triadimefon and triadimenol) were selected for which hepatotoxicity was considered as a common effect on which to establish a CAG. The mechanism(s) for hepatotoxicity remain to be determined.

In the present exercise, CAGs were limited to compounds with the triazole structure. However, in a full assessment, all compounds acting with the same mode/mechanism of action, should be included. In its previous Opinion, the Panel emphasised the need for common criteria throughout the EU for establishing a given CAG and this might be a task for the Panel in the future. The triazole exercise does demonstrate that whilst relatively broad criteria suffice for assembling a CAG from structurally-related compounds, it would be necessary to be more rigorous if all pesticides were to be potential candidates on the basis of a common toxicological effect, e.g. hepatotoxicity. In such circumstances, even the first tier would require some consideration of potential mode of action. In the case of the triazoles, the mechanism of pesticidal action was used as an initial surrogate for mode of action for mammalian toxicity.

6.1.2. Derivation of toxicological data for the HI and adHI approaches

It is recognized that, while risk assessments with single chemicals are typically based on the most sensitive adverse effect, this will not necessarily be true for cumulative risk assessments. Indeed, the common teratogenic effect was not always the most sensitive end-point for these seven triazoles. However, higher tier cumulative risk assessments must be based on the endpoint chosen as a direct consequence of the common mechanism, or at least for membership of the CAG. Therefore, end-point specific NOAELs were identified for each compound and end-point specific "ARfDs" were determined by applying the standard uncertainty factor (100). It should be noted that these uncertainty factors do not necessarily correspond to those used by the organisation that set the ARfD or to those suggested in the DAR (e.g. 250 diniconazole M, same end-point and 25 for triadimefon, different end-point).

It should be noted that triazoles are compounds that have been in use for many years and many of the studies used for the evaluations were old, in most cases not fully meeting current requirements. However, for evaluation of developmental toxicity most of the studies were based on the internationally accepted study protocol (OECD, 2001) and hence were comparable. The species of choice for developmental effects was the rat, but different strains were used, which may impact on the sensitivity of the effect. Other aspects that were not standardized included the dosing vehicle and group sizes.

In the definition of hepatotoxicity, different end-points for liver effects were used: changes in serum enzyme levels (increased ALT and AST activity), increased liver weights, hepatocellular hypertrophy, frequency of cytoplasmic lamellar bodies, mixed foci of cellular alteration and fatty change, significant centrilobular to midzonal hepatocellular enlargement and vacuolization. In this case, hepatotoxicity was the end point selected for setting the ADI of a number of individual compounds (i.e.: cyproconazole, difenoconazole, diniconazole M, epoxiconazole, propiconazole, triadimenol). For the other compounds, relevant NOAELs had to be identified and end-point specific "ADIs" were determined by applying the standard UFs (100 or, in the case of a LOAEL, 1000). In some cases species other than rats (mice, dogs) were used for selection of the end point. It should be noted that these UFs do not necessarily correspond to those used or suggested in the DAR (e.g. 250 for diniconazole M, same end-point).The HI for short and long term exposure is based on existing ARfDs and ADIs and the adHI is based on end-point specific ARfDs and ADIs (cranio-facial malformations or hepatotoxicity, respectively).

The RfPI approach was not used in the triazoles cumulative exposure assessment exercise, because the RfPI is equivalent to the adHI as the UF was 100 for all compounds.

6.1.3. Derivation of Relative Potency Factors (RPF)

In order to standardize the common toxicity for the compounds in the CAG, RPFs were initially estimated based on NOAEL (or 1/10 of LOAEL) relative to the NOAEL of an IC for both acute and chronic assessment. The selection of the IC in the triazole example was based on hazard considerations (well defined for common mechanism effect and responses for common toxicity consistent with that of group) and dose-response considerations (well characterized and with adequate dose-spacing between NOAEL and LOAEL).

6.1.4. BMD approach as a higher tier

A scientific refinement of this approach, where the data are adequate to support it, is represented by benchmark dose (BMD) modelling (EFSA, 2009). This was used for acute exposure assessment only, because no harmonized end-points could be identified for hepatotoxicity. The 5% response level was chosen because it is generally at or near the limit of sensitivity for developmental effects. This method required many details for modelling, which were not available in most DARs and the information had to be retrieved from the original reports of the developmental studies.

For four of the triazoles in the CAG, the RPF based on the BMD5 was higher than that derived from the NOAEL, though by not more than two-fold (see Table 3). This indicates that although the use of BMD represents a more refined step in the risk assessment it will not necessarily result in a reduction in the apparent risk. The use of BMD can produce a more consistent basis for comparing relative potencies as it identifies the dose that produces a defined (in the case of the triazole CAG, 5%) level of response. The use of the NOAEL is confined to one of the dose levels used in the study and is independent of the magnitude of any response above the NOAEL.

6.2. Exposure estimations

The estimations of the cumulative exposures to the triazoles are described in Section 3.4 – 3.9. The tiered approach as proposed in the previous opinion for exposure estimations includes 5 different steps of which the first three are based on deterministic estimations and the last two on probabilistic methodology (see Section 1.3, Figures 2 and 3). Four different scenarios (case studies) were investigated including acute and chronic exposure at actual and at MRL level, but not all 5 tiers were applied in the triazole exercise. In this exercise, it was recognized that tier 1 and tier 2 are not different tiers, but rather address different scenarios. Tier 1 is used for risk assessments of existing or proposed MRLs and tier 2 is used for risk assessment of actual exposures at monitoring levels. Furthermore the proposed tier 3 refers to inclusion of processing data. It was decided that this type of information should always be included when data are available and therefore a separate tier is not needed. Finally tier 5 refers to a different type of probabilistic exposure assessment where fraction of population instead of fraction of person-days is addressed. This is a possible refinement but it was not performed. In view of these findings, the Panel proposes a revision of the original tiered approach in Chapter 7. The remainder of this section discusses detailed findings from the current exercise. Some of these findings are of a general nature and apply equally to single pesticide and cumulative exposure assessments.

It was noted that not all 27 EU Member States have consumption data available. In particular, there is a lack of data from the new Member States (Elia et al., 2006).

6.2.1. Deterministic tiers

In the triazole exercise, the deterministic exposure estimations were made using consumption data from the EFSA PRIMo database (see Section 3.1) as input. The PRIMo database is accessible for all EU Member States and is an input tool for exposure estimation both at national and European level. In the triazole exercise, however, the PPR Panel encountered some limitations in this database.

The first limitation is the way that data on the consumption of processed foods have been handled by the different Member States. As explained in Section 3.2.5, consumption data in PRIMo represent the sum of all forms of the food through which the commodity is consumed after back calculation to the RAC, or data on the RAC as such. The PRIMo Large Portion database does not contain, or only contains very limited, information on consumption levels of processed foods as such (e.g. data on consumption of orange juice). Generally, processed foods contain lower residues than the RAC. When all forms of food have been back calculated to the RAC, it is not possible to refine the intake calculations by using processing factors to adjust the residue level for the processed food. On the other hand, when processed foods are not back calculated to RAC, and are not listed individually as well, processed foods are excluded from the calculations and contributors to the total exposure may be missed. Whether or not processed foods were included in the mean consumption figures again depends on the MS supplying the data. EFSA is presently undertaking efforts to include consumption levels of processed food in the PRIMo databases.

Furthermore, the deterministic approach taken as a starting point to assess acute cumulative exposure was developed for single chemical assessments and as such addresses only one RAC-pesticide combination at a time. Exposures via other foods or of other pesticides belonging to the same CAG are not initially included in the deterministic approach. The PPR Panel constructed a method for calculating the background levels of exposure via other foods and other pesticides as described in Section 3.4. The Panel calculated an average background level based on chronic exposure data (mean consumption level per food and mean residue level per food and pesticide) for the whole group of pesticides belonging to the same CAG. This may, however, not be a worst-case level of background exposure for acute exposure assessment. Further discussion and dialogue with risk managers is needed regarding the level of conservatism to be built into the acute deterministic approach regarding the background level.

Another concern is the use of the PRIMo database for deterministic chronic intake estimations. The consumption data included in the PRIMo databases are generally derived from food consumption surveys and are considered as realistic averages of levels consumed by a certain population. Previously, the usual or chronic exposure was estimated based on average statistics derived from Food Balance Sheets (FBS - a country's annual food production, plus imports and minus exports, divided by the number of inhabitants). It was recognised that average consumption from FBS was significantly higher than average consumption from real consumption diets (WHO, 1997a). In addition it was assumed that this overestimation using the FBS data was of such a magnitude that it compensated for a lack of information regarding the above average consumption data. However, using the chronic PRIMo model (IEDI equation) based on more realistic food consumption data, this compensation is lost. The PRIMo database does not include consumption data of above average consumption (it does include LPs in the acute database but these do not necessarily represent the appropriate choice for chronic assessments). It is noted that in the IEDI equation this underestimation on the consumption side is compensated by very conservative assumptions on the residue side. There is however no quantitative information on whether this balances out, and this should be further investigated.

Furthermore, not all commodities are included in the data sets of Member States that have offered their data to the PRIMo database. The possible contribution from missing commodities had to be estimated either by extrapolation from other commodities and/or other consumer groups. The WHO cluster diets were used a few times in this way during the triazole exercise[16]. The uncertainty introduced during such extrapolations will vary from case to case and the impact on the risk assessment has to be assessed for each case.

During the triazole exercise, it was also observed a few times that for some commodities for which consumption figures were included in the PRIMo database, no residue levels were available because they were not included in the monitoring programmes. Therefore, residue levels in these commodities had to be estimated by extrapolating levels analysed in similar commodities. The uncertainty introduced during

[16] The WHO diets are based on trade figures and they are therefore considered as an overestimation of the real consumption pattern

these extrapolations will vary from case to case and the impact on the risk assessment must therefore also be assessed on a case by case basis.

The PPR Panel appreciates the development of the PRIMo database. The establishment of a European database with consumption (and residue) data to be used for future health and risk assessments has a very high priority in the strategy of EFSA. The Panel is therefore confident that the PRIMo database will be updated and further developed as a better tool for future risk assessments of dietary intake of single residues and of cumulative exposures to mixtures of pesticides.

6.2.2. Probabilistic tiers

Probabilistic models are intended to result in more informative estimates of exposure compared to deterministic models. In an EFSA opinion on acute dietary exposure (EFSA, 2007b), probabilistic exposure results, representing the actual exposure, were compared to the level of protection as determined with the deterministic approach. Furthermore, a few probabilistic models have been validated against exposure levels that were calculated based on duplicate diets (Boon et al., 2003; Lopez et al., 2003).

Probabilistic models or MCRA simulations for acute exposure assessment make use of data on all the foods eaten by the same consumer per day and combine the amount consumed of each food item with a randomly drawn residue level analysed in the food concerned from the residue database. This principle is applied for all the consumers. All possible combinations of consumption amounts and possible residue concentrations will be dealt with providing that a sufficiently high number of iterations (e.g. 1,000,000) are performed. The probabilistic model for acute exposure assessment used in the exercise addresses all food items for each individual consumer simultaneously.

For chronic exposure calculations a slightly more complicated procedure is followed. Chronic exposure is defined as exposure over a life time or over a significant period in life. The consumption data available today, however, do not provide information of life-long consumption patterns of individuals. A typical consumption database contains food reported over a period of 2 up to 7 days for a particular individual. Providing that the daily exposure distribution (based on combining all daily consumption patterns with the mean residue level per food) is normally distributed after a log-transformation, and not bimodal and statistical models can be used to remove the within-person variation (variation between days per individual) from the distribution. Two models have been tested in the triazole exercise namely the ISUF method (Dodd, 1996; Nusser et al., 1996 and 1997) and the BBN method (de Boer and van der Voet, 2007; de Boer et al., submitted; Slob, 2006). Not all models apply in all cases and significant model uncertainty was observed in a few calculation scenarios.

When in the probabilistic model for a particular RAC-pesticide combination, MRLs or field trial data are used and monitoring data for other RAC-pesticide combinations, a bimodal exposure distribution can be expected. In such cases the lower part of the exposure distribution (first mode) relates to daily consumption consisting of only food items for which monitoring results are used, and the other part (second mode) to daily consumption of the particular RAC for which MRL, STMR or field trial data are used. In the case of a bimodal shaped daily exposure distribution, the ISUF and BBN models could not be used. Here, the individual exposure means were calculated based on the daily exposure distributions without removal of the within-person variation. This is referred to as the IOM (Individual Observed Mean) method and assumed to be conservative in the higher tails of the exposure distribution (van Klaveren et al., 2009). However more research is needed on how to model bimodal distributions.

The European project SAFE FOODS has resulted in an Electronic Platform in which national food consumption databases of the Netherlands, Sweden, Italy, Denmark and the Czech Republic were made compatible with the Monte Carlo Risk Assessment (MCRA) model (Boon et al., 2009). MCRA is one of the models that can be used to perform short- and long-term exposure calculations in a probabilistic way

(de Boer and van der Voet, 2007).[17] Once the food consumption data and monitoring data are organised in a comparable way and compatible with MCRA, pan-European pesticide assessments can be performed fairly quickly e.g. within hours (Boon et al. 2009). The PPR Panel refers to its previous opinion (EFSA, 2008a) for other probabilistic models which can be used for cumulative exposure assessment and providing similar performances.

The probabilistic approach addresses consumption of RACs eaten as such as well as of RACs consumed as part of processed food. Boon et al. (submitted) describe a procedure by which food consumption data can be converted back to consumption data at RAC level. This is relevant for making an optimal link between pesticides analysed at RAC level and consumption data. For this, for example, recipes of complex dishes and information from labels were used to determine the amount of RAC present in all foods reported in the food consumption database. The result is a database that links foods to their corresponding RAC ingredients, including their mass fraction. When using this information in an exposure assessment, each RAC – food combination can be linked to its correct variability and processing factor. For example, a variability factor of 3.6 was used when dealing with a tomato eaten as such, but a variability factor of 1 was used when tomato was consumed via ketchup. It is obvious that the processing factors will also differ between tomatoes eaten as such (e.g. washing) and as ketchup. In the probabilistic triazole exercise and the EU-project SAFE FOODS, foods reported in the food consumption databases of Sweden, United Kingdom, Denmark, Czech Republic, France, The Netherlands and Italy were converted to RAC level in a comparable way (Boon et al., submitted; van Klaveren et al., 2009).

Probabilistic modelling as used in the triazole exercise was found to be informative regarding the whole acute and chronic exposure distributions aiming at estimating either the actual exposure or the potential exposure in the MRL setting process. The MCRA model includes exposure via both RACs eaten as such, and as ingredients of processed foods (like pizza, ketchup, juices, etc). Furthermore, MCRA can provide information on the RACs and pesticides of the CAG that contribute most to the (average) cumulative exposure. It also provides, for a certain percentile of exposure as selected by the risk assessor, information on the consumers present around this percentile, including amount consumed, pesticide residue level selected from the monitoring residue database, body weight, age, etc. This information is important for reasons of transparency. Each possible exposure level can thus be checked.

The results of the probabilistic modelling exercise provided an overview of the variation in consumption patterns in different parts of Europe and showed that selections from the databases can be made to focus the exposure assessment on special groups, like children and babies. The Electronic Platform of individual food consumption databases (harmonised at RAC level and linked to probabilistic software) as constructed in the EU -project SAFE FOODS, and expanded in the probabilistic triazole exercise by including more countries, can be used for future cumulative risk assessments provided that access to the data and models is possible.

It was recognized that in some countries the same triazoles were analysed in different RACs. However, in other countries different triazoles were analysed between RACs but also within one RAC. This very much hampered the use of one of the cumulative models applied in the exercise (Van Klaveren et al. 2008). It is therefore recommended that either a harmonized way of collecting residue data including requirements for residue data generation in Europe with respect to cumulative risk assessment should be given in guidelines or the modelling approach should be optimized when the same pesticides belonging to the same CAG are not analysed. Further model development at European level is envisaged.

6.2.3. Quality of the monitoring data and sensitivity analyses

The quality and reliability of the exposure estimations and consequently also of the risk assessment depend substantially on the availability and quality of the pesticide residue and consumption data, and the methodology used to assess the exposure (deterministic or probabilistic). Monitoring data are primarily

[17] The model can be accessed via the Internet (https://mcra.rikilt.wur.nl/www….). There is a guideline for the user and a reference manual describing and justifying the statistical assumptions in the model (De Boer and Van der Voet 2007).

generated as part of Member State monitoring programmes. An important requirement to ensure the quality of the monitoring results is that the analysing laboratories hold an ISO17025 accreditation.

When assessing the quality of monitoring programmes and the resulting residue data, it is important to be aware that in addition to random sampling procedures, usually (some) targeted sampling is undertaken based on, for example, the violation rate in previous years. The degree of targeted sampling is usually not reported. It is also important for the interpretation of the estimated exposures to be aware that monitoring programmes never include all pesticides present in the worldwide market and that the residue data typically do not include the whole range of commodities consumed. Due to this, extrapolation of residue levels between commodities may be needed.

However, a major concern associated with monitoring data is the high percentage of samples with a residue level below the LOR, the so-called NDs. The handling of such data (see Section 3.2.7) can have a great impact on the exposure assessment, as discussed in Chapter 5. It should be added that the handling of NDs has been one of the key points in the discussions on how to calculate the cumulative exposures in the different case studies. For the triazole exercise, exposures have been calculated under different assumptions regarding the residue level to be assigned to the NDs. The PPR Panel decided to assign ½LOR to the NDs for commodities with at least one positive finding in the deterministic estimations. The residue levels in ND samples of other commodities were assumed to be zero. Based on the considerations and experiences from the triazole exercise, the PPR Panel concludes that it is very important that an appropriate and standardised way of handling non-detects is established in order to ensure the reliability and recognition of the exposure estimates and the subsequent risk assessments.

6.3. Risk characterisation

Based on the estimated exposures, risk characterisations of cumulative exposures to the triazoles were performed for four different scenarios following the proposed methodology (Chapter 1). At the different tiers of exposure estimations, the risk was assessed by calculating the HI, the ad-HI and the RPF-adjusted exposures expressed as a percentage of the toxicological RV (ADI or ARfD for common effect) of the IC. Actual exposure and MRL setting were addressed.

It is known and also illustrated by the results of this exercise that risk assessments of cumulative exposure based on adHI and RPF adjusted exposures mathematically coincide (within rounding errors) when the UFs used to establish the toxicological RVs are the same for all pesticides of the CAG (see Appendix L). Thus, in this situation, only one of the two tiers is needed for risk assessment. The PPR Panel is of the opinion that the adHI should be the preferred approach, since it makes the contribution of the individual pesticides of the CAG more transparent.

As discussed in the Panel's earlier Opinion, the method chosen for cumulating hazard makes little difference when the NOAELs have been obtained in comparable studies and the same UFs are used in deriving RV. However, when different UFs have been used in deriving RVs, the outcome of the calculation will depend upon the method chosen. For example, if human data are used to derive some RVs values (using an UF of 10) and data from experimental animals to derive the other RVs (with an UF of 100), the adHI and the RPF approaches will give different results, as will the use of an IC with a RV based on an UF of 10 compared with one based on an UF of 100. Whilst this is reasonable and justifiable from a toxicological point of view, it will result in discrepancies when performing CRA. When determining the RPF, the Panel emphasised in its earlier Opinion the need, where possible, to obtain RfPs (e.g. NOAELs) in the same species under similar experimental circumstances. A pragmatic solution to the situation where different UFs have been used in the derivation of RVs is to correct the NOAELs (or other reference points such as BMDs) for any difference in the uncertainty factors used prior to calculation of the RPFs (see EFSA, 2008a).

The PPR Panel recognised that using the HI approach would have saved time and discussion in the identification of the RfP and the derivation of the end-point specific reference value. For instance, selecting all compounds causing cranio-facial malformations (or any developmental effect) and using the RV

(any end-point) to be used for regulatory purposes would have resulted in acceptable estimates of exposure in most of the scenarios, and hence no further step in tiered approach would have been needed. However, the PPR Panel decided, for the worked example, to also illustrate the use of the adHI. It is noted, however, that the HI approach might be an easy and relatively quick screening step for prioritisation of CRA.

Overall, the completed risk assessments of the worked example illustrate the need and the strength of the proposed tiered methodology for risk assessment of the cumulative exposure to pesticides. The triazole example shows that in some cases at the lowest tier an unacceptable risk cannot be excluded, whereas at higher tiers a more definitive answer can be found.

6.4. Tiered approach

In the first EFSA opinion regarding cumulative exposure a tiered approach was proposed (EFSA, 2008a). In other guidelines similar proposals have been made (WHO, 2008b). The proposed methodology for cumulative dietary exposure to pesticides was tested in four different scenarios including estimations of chronic and acute exposure at actual level and for MRL setting.

The worked example proved to be very valuable in testing the tiered methodology and identifying further necessary steps before its routine application would be possible.

Definition of the CAG

The establishment of relevant CAGs is the starting point for all cumulative risk assessments. In its earlier opinion (EFSA, 2008a), the PPR Panel proposed that refinement of the CAG should be an option at every tier. However, in practice this would prove to be too labour intensive, necessitating multiple reruns of the exposure estimates. The Panel therefore concluded that the tiered approach could be simplified by starting with a CAG as refined as the data allow, and using the same CAG in all steps of the assessment. However, consensus should be reached at an international level on which criteria and which compounds should be used to put together a CAG, to avoid discrepancies between national cumulative risk assessments. In some cases, the CAG used in a cumulative risk assessment may be based on relatively broad criteria, for example a common target organ due to lack on information on mode or mechanism of action for the common toxicological effect. In such circumstances, should a cumulative risk assessment fail to provide adequate reassurance, according to criteria agreed with risk managers, consideration will need to be given as to whether the data would support inclusion of some adjustment for the conservatism in the assessment, or to suspend a final decision until sufficient information on mode or mechanism of action is available to enable refinement of the CAG.

Hazard assessment

A general principle of tiered approaches is that a first tier should be more conservative compared to higher tiers. The Panel concluded that this principle is satisfied by the proposed tiered approach for hazard assessment. The BMD should be considered as a refinement within the same tier and would be used for example when the acceptability of the assessment using the NOAELs is borderline (see Chapter 7). The Panel concluded that, with this modification, the proposed hazard assessment tiers are clear and could be performed for any CAG.

Exposure assessment and risk characterisation

An essential requirement of any assessment methodology is that it provides an appropriate level of protection. The Panel identified several issues that might affect the level of protection achieved by the proposed methodology, including the estimation of background exposure in the deterministic assessments and the treatment of NDs in both deterministic and probabilistic approaches. Ideally, the level of protection would be confirmed by comparison with empirical measurements of exposure and risk, but in practice this is not possible. Another option is to evaluate the level of protection of lower tier procedures by comparing them with the results of higher tier methods, on the basis that the latter are expected to be more realistic. An example of this is provided by the Panel's previous opinion, which examined the level of protection provided by the IESTI equation for acute dietary exposure to individual pesticides (EFSA, 2007b). A similar calibration is needed in order to evaluate the appropriateness of the proposed deterministic approach for cumulative assessments, by comparing them with probabilistic estimates. A start can be made on this with the results for triazoles in the present opinion, although they are limited to a single CAG and it cannot be assumed that the probabilistic estimates are correct as they are also affected by many uncertainties (see Chapter 5). However when comparing the deterministic and probabilistic results it must be remembered that they were based on different assumptions for the handling of NDs.

It is noted as a general point that the approach used for probabilistic estimations of cumulative exposures is based on the RPFs. This allows that the contributions from the individual pesticides of the CAG can be combined in a proper way. However, it necessitates definition of RPFs as a prerequisite for the probabilistic estimations. Therefore, risk assessments based on probabilistic exposure estimations is in practice usually at tier C-4 and D-4 whereas tier A-4, B-4, A-5 and B-5 are less likely to be used (see tiers table 26).

Four exposure scenarios were considered to be relevant for cumulative risk assessment. For each scenario, the Panel evaluated both deterministic and probabilistic approaches and considered their suitability for use in a tiered approach. The Panel's conclusions for each scenario are set out below.

Scenario 1 – Actual acute exposure

This scenario addresses actual exposure (i.e. from the patterns of usage that actually occur in practice), during an acute (i.e. 24 hours) time span.

As described in Section 3.6, the PPR Panel identified 2 possible subscenarios under the assessment of actual acute exposure.

In order to meet the purpose of sub-scenario 1 (routine evaluation of all available monitoring data at total population level), the Panel's probabilistic assessments estimated the full distribution of acute exposures, reflecting the full distributions of both consumption and residues. The results were reported as %ARfD of the index compound at different percentiles of person-days, from the 95th to the 99.99th percentile.

In order to meet the purpose of subscenario 2, deterministic cumulative assessments were performed to address the risk of specific consumers exposed to commodities containing high residue levels (critical commodity concept). The Panel recognise that the deterministic methodology can also address the risk

related to individual commodity samples containing more than one pesticide of the acute CAG (co-occurrence events).

The Panel did not identify a deterministic methodology which would be appropriate for addressing subscenario 1. This is due to the intrinsic nature of the deterministic approach making impossible to appropriately determine how to combine a vast range of commodities and residue levels for this subscenario. Nevertheless, under the conditions of this exercise, where actual acute exposure assessment demonstrate a low level of risk, the critical commodity approach gave results containing some predictive information for subscenario 1 with an appropriate level of conservatism (in the sense that the deterministic estimates for at least some commodities exceed the 99.99th percentiles of the distribution estimated by the probabilistic approach as shown by comparison of tables 27-28 and 29)18. For this reason, the PPR Panel notes that in principle consideration can be given to using the critical commodity approach as a pragmatic first tier for subscenario 1.

However, it is not possible to say whether the deterministic approach would be conservative in general, i.e. for other CAGs / other classes of pesticides.

Scenario 2 – Actual chronic exposure

Scenario 2 assesses actual exposure during a chronic time span (i.e. lifetime).

The Panel's probabilistic assessments for this scenario estimated the full distribution of chronic exposures, reflecting the full distributions of both consumption and residues.

The Panel's deterministic assessments for scenario 2 uses mean residues combined with estimates of average consumption from the PRIMo database. However, the estimates in the PRIMo database are averaged across all consumers (including non-consumers), and would therefore be unconservative if risk managers wish to protect high consumers19. The Panel recommends further discussion on the desired level of protection.

The results of the present case study indicate that, for triazoles, the deterministic approach using the PRIMo database was more conservative than the probabilistic approach, in the sense that the deterministic estimates exceed the 99.99th percentiles of the distribution estimated by the probabilistic approach (compare Tables 31 and 32). However, it must be remembered that the probabilistic assessment used a less conservative approach to NDs[20], and the over-all conservatism of the probabilistic assessment is also uncertain. Furthermore, as for scenario 1, it is not possible to say whether a similar relationship between the deterministic and probabilistic estimates would be obtained for other CAGs / other classes of pesticides.

Scenario 3 – Acute MRL-setting

[18] Note that although the deterministic exposure assessment and the probabilistic exposure assessment use different assumptions and address different subscenarios (see 3.6) the probabilistic exposure assessment nevertheless represents an (uncertain) estimation of the full distribution of actual acute exposures and can therefore provide an (uncertain) indication of the level of protection that would be achieved if the deterministic exposure assessments were to be used for risk assessment purposes in sub-scenario 1.

[19] In the chronic dietary risk assessment methodology for single chemicals as established by WHO, the IEDI equation uses consumption values based on Food Balance Sheets, which are recognised to represent above-average consumption. PRIMo however uses the IEDI equation with average consumption values derived from food consumption surveys, which are more accurate values, therefore leading to less conservative results.

[20] As explained in section 5.1, the handling of non-detects has a major impact (2 to 3 orders of magnitude) on the estimated background exposure (actual chronic exposure). Therefore the PPR Panel also compared the outcome of deterministic and probabilistic approaches for actual chronic exposure, under the same assumptions for non-detects samples. A comparison between Tables 32 and 41 (Scenario I for handling of non detects) show that for Dutch children, the deterministic estimation of actual chronic exposure is about 2 times higher than the mean of the probabilistic exposure distribution, but significantly lower than the exposure at high percentiles, when non detects are all considered as 0. Although more experience is needed before deriving firm conclusions, this supports the concern expressed in sections 3.7.1 and 3.10 that the deterministic approach used in the actual chronic exposure scenario may not meet the desired level of protection of Risk Managers.

Scenario 3 assesses 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.

The Panel's deterministic assessments for scenario 3 were conducted by combining exposure at the MRL for the pesticide/commodity combination under evaluation with an estimate of background (average) exposure from all other pesticide/commodity combinations.

The Panel's probabilistic assessments for scenario 3 estimate the full distribution of theoretical acute exposures for person-days in which the commodity under evaluation is consumed, assuming that this commodity contains a residue of the compound under evaluation at the level of the relevant MRL, and using monitoring data for residues in other compound/commodity combinations.

The results of the present case study indicate that, for triazoles, the deterministic estimates ranged between the 95th and the 99.99th percentiles of the distribution estimated by the probabilistic approach (compare Tables 33-36). It is noted that the probabilistic assessment used a less conservative approach to NDs, and the over-all conservatism of the probabilistic assessment is also uncertain. Furthermore, it is once again not possible to say whether similar results would be obtained for other CAGs / other classes of pesticides.

It should be noted that the setting of MRL-values for a pesticide can involve one or several commodities. In the triazole exercise the tiered approach was only tested for the MRL-setting of one pesticide/commodity at a time. It is recommended that the methodology is likewise tested for MRL-setting of several pesticide/commodity combinations at the same time.

Scenario 4 – Chronic MRL-setting

Scenario 4 assesses chronic (i.e. lifetime) exposure relevant for MRL-setting, with the compound/commodity combination under evaluation at the level of the STMR.

The Panel's probabilistic assessments for scenario 4 estimate the full distribution of theoretical chronic exposures for person-days in which the commodity under evaluation is consumed, assuming that this commodity contains a residue of the compound under evaluation at levels observed in supervised residue trials, and using the average of monitoring data for residues in other compound/commodity combinations.

In scenario 4, the distribution of intakes will usually be bimodal due to the combination of one compound/commodity combination at relatively high levels (field trial results) with others at background levels. In these cases, the Individual Observed Means (IOM) model should be used, because the other models are not appropriate when the distribution of intakes is bimodal. As mentioned above, this should generate conservative results in the upper percentiles, provided that the consumption survey and monitoring datasets on which the intakes are based are large enough to be representative of low-frequency combinations of consumption and residues.

The Panel's deterministic assessments for scenario 4 were conducted using the PRIMo model for chronic intakes, using the STMR as the residue level for the commodity under evaluation, and average residues from monitoring for all other pesticide/commodity combinations.

The results of the present case study indicate that, for triazoles, the deterministic estimates ranged from below the 90th to above the 99.99th percentiles of the distribution estimated by the probabilistic approach (compare Tables 37-39). However, different handling of NDs makes it difficult to compare the deterministic and probabilistic results. It is noted that the probabilistic assessment used a less conservative approach to NDs, and the over-all conservatism of the probabilistic assessment is also uncertain. And again, it is not possible to say whether similar results would be obtained for other CAGs / other classes of pesticides.

As for scenario 3, it is noted that the setting of MRL-values for a pesticide can involve one or several commodities. In the triazole exercise the tiered approach was only tested for the MRL-setting of one pesticide/commodity at a time. It should be further investigated if the methodology needs to be expanded for MRL-setting of several pesticide/commodity combinations at the same time.

Conclusion on tiered approach

The results of the triazoles exercise provide a useful first insight into the relative conservatism of the proposed deterministic and probabilistic approaches to exposure assessment. However, as emphasised above, it is not possible to say whether similar results would be obtained for other CAGs or other classes of pesticides. Therefore, it is not possible to draw general conclusions about the level of protection provided by the deterministic approach. Furthermore, some issues affecting the probabilistic approach require further research (in particular methods for dealing with bimodal distributions of intakes). General issues concerning the use of probabilistic modelling are currently being considered in another mandate, in which the Panel is developing a guidance document for the use of probabilistic modelling for exposure assessments for single chemicals. Taking all these factors into consideration, the Panel concludes that it would be premature to introduce either the deterministic or probabilistic approaches for cumulative risk assessment into routine regulatory use at this time. Recommendations for next steps to enable routine application are considered in Section 7.

6.5. Practicalities of the different tools/approaches

As for individual pesticides, risk assessment of cumulative dietary exposure to pesticides will be encumbered with uncertainties to varying degrees as described in Chapter 5. Besides the uncertainty, such risk assessments can also be a rather difficult and time-consuming process. The difficulties and time are primarily related to retrieval of the data needed for hazard characterization and exposure estimations and the time needed to insert data into the models used for exposure calculations. It is obviously a prerequisite that the models for deterministic and/or probabilistic exposure estimations are available and easy to use. This is the case for the EFSA PRIMo model, whereas models for probabilistic exposure estimations even when available require training to be used properly. Table 45 is intended to give an overview based on the triazoles exercise of the workload and difficulties connected to the different tools and approaches of the process. The table gives the workload as low, medium or high, but it should be emphasized that it will change from case to case.

Table 45. Workload of steps in the tiered approach.

Approaches	Tool	Work-load/Expertise level	Comments
Identification of CAG	Chemical structure and mode of pesticidal action:	Low/Medium	Rather easy and not time-consuming, depending on the compound
	Common toxic effect for short-term risk assessment (cranio-facial malformations)	Medium/High	Required review of details in original developmental studies, and sometimes scientific articles
	Common toxic effect for chronic risk assessment (hepatotoxicity)	Medium /High	Required some discussion between experts to identify relevant end-points and therefore was more time-consuming (study summary, and sometimes original studies and scientific articles)
	Assessment of the mechanism of action	High	Requires expert judgement and exhaustive literature review
Hazard Characterisation	ADIs and ARfDs	Low	Values will normally be available at the EU database and WHO website
	NOAEL for common effect	High	Might involve intensive and time consuming review of the toxicological databases and literature
	Adjusted ADIs and ARfDs for common effect	Low	Investigate whether UF other than 100 is needed
	BMD for common effect	High	Might involve intensive and time consuming review of the toxicological databases. Requires access to and knowledge of BMD software
	RPFs – selection of Index Compound	Medium	The RPFs are easily calculated when the NOAELs/BMDs are established. Selection of Index Compounds involves an intensive review of the toxicological database
Consumption data	National, deterministic	Low to high	Depending on country. Countries with consumption data already included in PRIMo, low. Countries with no data, high
	European, deterministic	Low to High	No information on processed foods in PRIMo. No information for eastern EU MS
	National, probabilistic	Low to high	Depending on country. Several countries are now organized in SAFE FOODS: low. New countries to be added: high
	European, probabilistic	Low to High	Depending on country. Several countries are now organized in SAFE FOODS: low. New countries to be added: high

Table 45. Workload of steps in the tiered approach (cont.)

Approaches	Tool	Workload	Comments
Residue data	MRL-values	Low	EU MRL-values are available at the website of the EU COM
	Monitoring data	High	Only summary data at EU level. Monitoring data are available at the national level (more extensive than EU level) and at the EU level via EU COM website. National level: different for each country whether easy to find or not, national datasets might be incomplete making it necessary to extrapolate from other crops or countries
	Field Trial Data STMR-values	Medium	Data are not easily available but can be retrieved from the DARs and from the JMPR monographs via the Internet
	Processing Factors	Low to high	If processing factors are available, than low, if not than high. Many processing factors derived by JMPR and EU (DAR) are listed on the BfR website. Extrapolation from other countries might be associated with a rather high uncertainty. With the exception of drying (e. g. peppers – dried peppers, grapes – raisins), default factors are not recommended.
Exposure estimations	Deterministic	Medium to high	Only average data for residue levels need to be inserted in the PRIMo model, which is rather fast and easy to use. However, separate calculations of the contributions from each pesticide to the cumulative exposure might be rather time consuming. Calculation of RPF-adjusted exposures is easily performed when the RPFs are set. Depends also on number of pesticides in CAG, and number of scenarios that need to be addressed
	Probabilistic	Low to high	All individual data for consumption and residue levels need to be inserted in the probabilistic model, which is rather time consuming. However, the contributions from each pesticide to the cumulative exposure are an integral part of the model. Probabilistic calculation of RPF-adjusted exposures is likewise easily performed when the RPFs are set. When new data have to be organized, the workload is high.

Table 45. Workload of steps in the tiered approach (cont.)

Approaches	Tool	Workload	Comments
Risk characterisation	Deterministic/probabilistic	Low to high	When the toxicological reference values (for common effect) are established and the cumulative exposure (direct or adjusted) is estimated, the risk characterisation in terms of a comparison of the exposures to the reference values is a fast and easy task, which is an integral part of the deterministic and probabilistic models. Integrating all the uncertainties related to starting assumptions and input parameters however requires high level of expertise.

MRL and STMR levels are relatively easily accessible. However, it became clear that field trial data are currently not readily available, although they can be extracted from JMPR reports and the DARs produced for Annex I inclusion evaluations under Directive 91/414/EEC. However, EFSA's PRAPeR Unit is building a database in relation to Reg. 396/2005 and field trial data will be contained in this database.

DARs are available at the CIRCA-network,[21] which is accessible for the national authorities of the Member States. Retrieval of realistic processing factors seems even more difficult especially because these factors can sometimes vary from country to country depending on the local processing methodologies. It is noted however that an extensive inventory of processing factors gathered from DARs and JMPR reports is available at the BfR website[22]. The PPR panel concludes that scientific based guidance on processing factors in the form of a list – if possible - of recommended processing factors for different types of pesticide/commodities and types of processing will be an advantage, not only for cumulative dietary exposures but also more generally for estimation of dietary exposure to single pesticides.

Higher tier assessments are assumed to be increasingly more realistic. However serious drawbacks from higher tier assessments have been noted in the past, such as a lack of access to models, the computer time and capacity needed to perform these assessments, and the skills to organise consumption and residue databases in connection to the probabilistic models. The PPR Panel recognizes that much work has been carried out during the last five years to overcome these drawbacks and is aware that more work is and will be carried out in this area. Nowadays probabilistic models can be used via the Internet and are readily available and easy to use. Once the food consumption and residue databases are organized, pan-European modelling could be performed in a user-friendly way (Boon et al., 2009). However, proper expertise/training is still needed to decide on input data and to interpret the results obtained.

Furthermore, results of probabilistic exposure estimations are considered more complex than those of deterministic approaches. However, they are more informative especially when multiple commodities and pesticide residues are to be addressed. Probabilistic models provide insight into the distribution of the exposure within a consumer group, as well as information on the foods and pesticides that contribute most to the cumulative exposure. Such information should be very useful for risk managers.

[21] Some are available from EFSA on request for everyone via the web-side of EFSA: http://www.efsa.europa.eu/EFSA/ScientificPanels/PRAPER/efsa_locale-1178620753812_DraftAssessmentReports.htm
[22] http://www.bfr.bund.de/cd/579

CONCLUSIONS AND RECOMMENDATIONS

The PPR Panel concluded that there are still several issues that need to be addressed before the cumulative risk assessment methodology can be applied routinely. The main limitations are that there is not yet EU-wide consensus on the composition of relevant CAGs, the level of protection provided by the exposure assessments is uncertain, and that some details of the exposure methodology require further work (see Section 6.4).

Based on the findings of the triazole exercise, the Panel recommends that the tiered-approach that was proposed in its previous opinion (EFSA, 2008a) should be modified and simplified as shown in Figures 7 and 8 and Table 46, in order to enable efficient use of the deterministic and probabilistic approaches when they are ready for use. It should be noted that the schemes illustrated are not intended to be prescriptive and as already indicated, the assessor can enter at any tier, and jump by as many tiers, as the data and resources permit. In general, the higher the tier, the lower the uncertainty. Some options will give the same value numerically, if the same uncertainty factor is used for all compounds in the CAG, for example tiers 2 and 3a in figure 7. However, there are differences in the calculations involved, tier 2 involving the HQ and tier 3a the selection and use of an IC. Hence, there may be a preference for one of these tiers over the other, depending on circumstances.

Figure 6. Revised proposal for tiered hazard assessment.

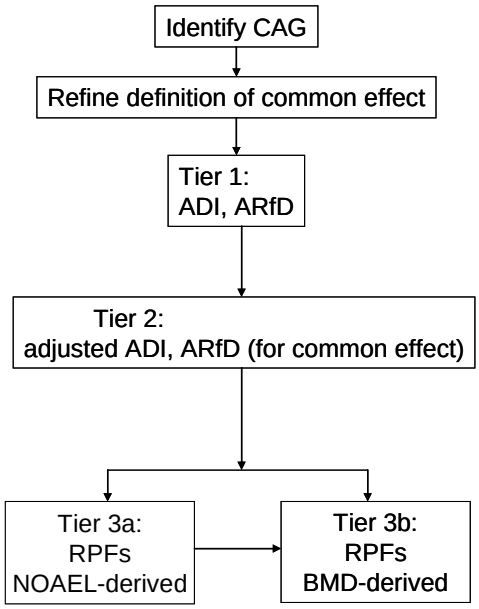
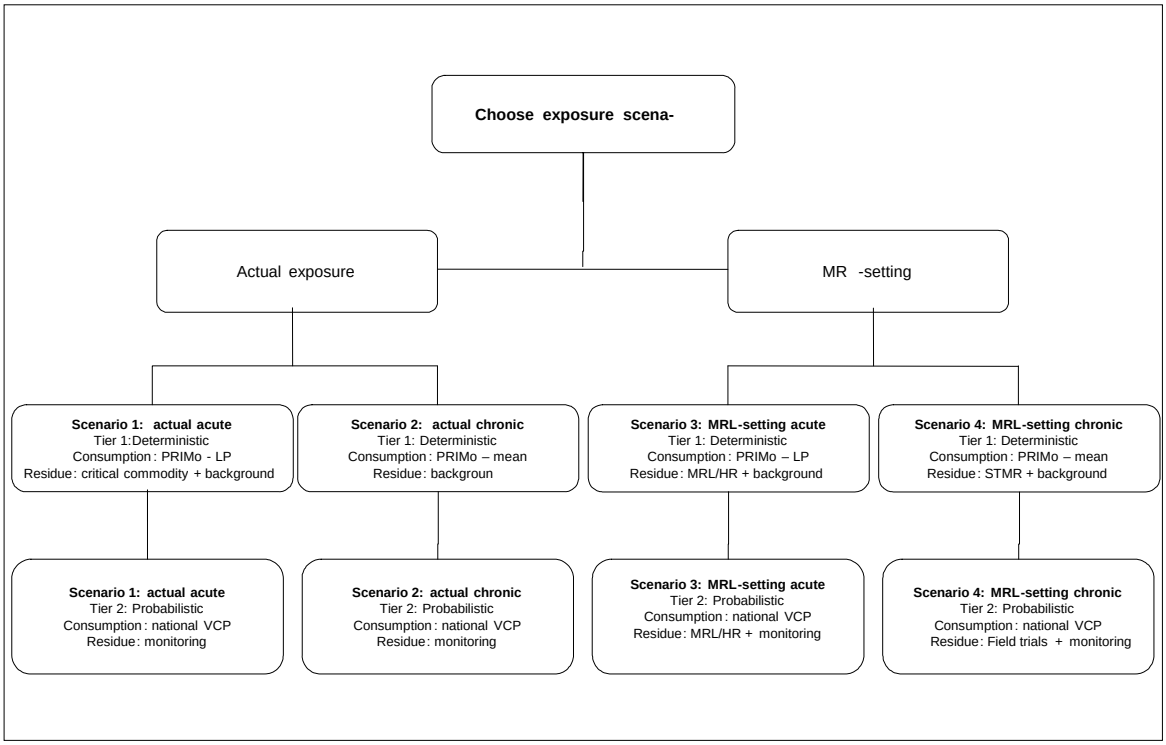


Figure 7. Revised proposal for tiered exposure assessment



The final risk assessment can be performed according to the scheme below:

Table 46. Overview of possible tiers in cumulative risk assessment. Please note that the scheme has to be worked through for each of the identified exposure scenarios: actual_acute, actual_chronic, MRL-setting_acute and MRL-setting_chronic[23].

Hazard	Exposure	
	Deterministic	Probabilistic
ADI, ARfD	HI – A1	HI-A2
Adjusted* ADI, ARfD	adjusted HI - B1	adjusted HI - B2
NOAEL*/ BMD*	RPF-C1/D1	RPF –C2/D2

* for common effect

[23] It should be noted that although combinations C1, D1, and A2 are in principle possible, they will normally not be the first choice. More often, a first tier hazard assessment will be combined with a first tier exposure assessment (A1, B1), and a refined hazard assessment will be combined with a refined exposure assessment (C2, D2).

Finally, the Panel makes the following recommendations for further development of the cumulative assessment approaches:

- The PPR Panel recommends that consensus should be reached at an international level on which criteria and which compounds (active substances and metabolites) should be included in CAGs, to avoid methodological differences between national cumulative risk assessments. As part of this, it should be noted that the EU-ADI and ARfD are established by consensus. The adjusted ADI or adjusted ARfD would possibly not be widely accepted. Therefore the Panel recommends that EFSA should coordinate the work to identify CAGs, and to derive the appropriate RVs, as is done for the standard RVs.

- The PPR Panel is currently developing guidance for probabilistic modelling 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 or by identifying with Risk Managers the appropriate percentile of consumption to address).

- Probabilistic modelling for the chronic MRL-setting scenario requires attention because a bimodal exposure distribution can be expected. Two of the models used for long-term cumulative exposure assessment could not deal with bimodal distributions in a statistically sound way. As a fallback option a third probabilistic model, the Individual Observed Means was introduced which can deal with bimodal distributions. However the IOM method tends to generate conservative results in the upper percentiles, provided that the consumption survey and monitoring datasets on which the intakes are based are large enough to be representative of low-frequency combinations of consumption and residues (which can be expected to be more influential in cumulative assessments than in assessments of single compounds). More research is needed on how to model bimodal distributions in a less conservative way.

- Further development of the PRIMo database and PRIMo model by inserting consumption data regarding processed food and above average food consumption levels.

- Further guidelines should be developed on how intake through processed foods should be included into the exposure assessment.

- Refined approaches for dealing with non-detects in both deterministic and probabilistic assessment should be investigated by cooperating with the DATEX Unit on the development of guidance on the handling of left-censored data.

- It is recommended to ensure that models and necessary data for probabilistic exposure estimations are made available and accessible for all stakeholders involved in cumulative risk assessments.

- Monitoring data should be generated and/or reported in a harmonized way e.g. so that the reporting includes analysis for all pesticides of interest in all samples. Furthermore, LORs should be standardized at a suitably low level.

- Further integration of BMD modelling and exposure modelling will be useful to quantify some of the uncertainties and might also result in a better understanding of the margin of exposure or margin of safety.

- MS have not derived LPs and mean consumptions, as provided for PRIMo, in the same way. The background of these numbers should be clarified.
- The Panel notes that there are many uncertainties affecting residues, consumption and toxicological values. Some of the uncertainties could be quantified.
- The issue of co-occurrences in deterministic exposure assessments should be further evaluated (over or under estimation).
- The setting of MRL-values for a pesticide can involve one or several commodities. In the triazole exercise the tiered approach was only tested for the MRL-setting of one pesticide/commodity at a time (scenarios 3 and 4). It should be explored whether the methodology needs to be expanded for MRL-setting of several pesticide/commodity combinations at the same time.

DOCUMENTATION PROVIDED TO EFSA

1. Background and Terms of Reference for the "Opinion of the Scientific Panel on Plant Protection products and their Residues to evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of regulation (EC) No. 336/2005, (Question N° EFSA-Q-2006-160)".

REFERENCES

Anonymous, 1998. Zo eet Nederland 1998. Resultaten van de voedselconsumptiepeiling 1997-1998 (Results of the Dutch National Food Consumption Survey 1997-1998). Den Haag, Voedingscentrum.

Becker, W., 1999. "Riksmaten 1997 - 1998. Svenskarna äter nyttigare - allt fler väljer grönt (Riksmaten 1997- 998. The Swedes eat more healthy)." Voar Föda 51, 24-27.

Becker, W. and Pearson, M., 2002. Riksmaten 1997-98. Dietary habits and nutrient intake in Sweden 1997-98. The second national food consumption survey. Uppsala, National Food Administration.

Boggio, V., Grossirod, A., Guyon, S., Fuchs F. and Fantino, F., 1999. Consommation alimentaire des nourrissons et des enfants en bas ages en France en 1997. Archives Pediatriques 6, 740-747.

Boon, P.E., van der Voet, H. and van Klaveren, J.D., 2003. Validation of a probabilistic model of dietary exposure to selected pesticides in Dutch infants. Food additive and Contaminants 20, Suppl. 1, 36-49.

Boon, P.E., Tjoe Nij, E.I.M., Koopman, N. and van Klaveren, J.D., 2004. Dietary habits and exposure to pesticides in Dutch infants (2004.017). RIKILT - Institute of Food Safety, Wageningen UR.

Boon, P.E., Ruprich, J., Petersen A., Moussavian, S., Debegnach, F, van Klaveren, J.D., (submitted). Harmonisation of food consumption data format for dietary exposure assessments of chemicals analysed in raw agricultural commodities.

Boon, P.E., Svensson, K., Moussavian, S., van der Voet, H., Petersen, A., Ruprich, J., Debegnach, F., de Boer ,W.J., van Donkersgoed, G., Brera, C., van Klaveren, J.D. and Busk, L., 2009. Probabilistic acute dietary exposure assessments to captan and tolylfluanid using several European food consumption and pesticide concentration databases. Food and Chemical Toxicology, doi:10.1016/j.fct.2009.01.040

Chen, P.-J., Padgett, W.T., Moore, T., Winnik, W., Lambert, G.R., Thai, S.-F., Hester, S.D. and Nesnow, S., 2009. Three conazoles increase hepatic microsomal retinoic acid metabolism and de-

crease mouse hepatic retinoic acid levels in vivo. Toxicology and Applied Pharmacology, 234(2), 143-155.

Codex (Codex Alimentarius Commission), 2007. Procedural Manual 17th Edition. <http://www.codexalimentarius.net/web/procedural_manual.jsp>

de Boer, W.J. and van der Voet, H., 2007. MCRA, Release 6. A web-based programme for Monte Carlo Risk Assessment, Biometris and RIKILT-Institute of Food Safety, Wageningen UR, Wageningen and National Institute for Public Health and the Environment (RIVM), Bilthoven.

de Boer, W.J., van der Voet, H., Bokkers, B.G.H., Bakker, M.I. and Boon, P.E., (submitted). A comparison of two models for estimating usual intake when consumption data include many zeros.

Dodd, K.W., 1996. A technical guide to C-SIDE (96-TR 32). Ames, Iowa: Department of Statistics and Center for Agricultural and Rural Development, Iowa State University. Available at:www.card.iastate.edu/publications/DBS/PDFFiles/96tr32.pdf

EC (European Commission), 2008. Guidelines on comparability, extrapolation, group tolerance and data requirements for setting MRLs. Health & Consumer Protection Directorate (SANCO). Doc. 7525/VI/95-rev.8 (01/02/2008). <http://ec.europa.eu/food/plant/protection/resources/app-d.pdf>

EFSA (European Food Safety Authority), 2005. Opinion of the Scientific Panel on Plant health, Plant protection products and their Residues on a request from Commission related to the appropriate variability factor(s) to be used for acute dietary exposure assessment of pesticide residues in fruit and vegetables. 16 February 2005. The EFSA Journal (2005) 177, 1-61

EFSA (European Food Safety Authority), 2006a. Guidance of the Scientific Committee on a request from EFSA related to Uncertainties in Dietary Exposure Assessment. 14 December 2006. The EFSA Journal (2006) 438, 1-54.

EFSA (European Food Safety Authority), 2007a. Reasoned opinion on the potential chronic and acute risks to consumers' health arising from proposed temporary EU MRLs according to Regulation (EC) No 396/2005 on maximum residue levels of pesticides in food and feed of plant and animal origin. 15 March 2007. The EFSA Journal (2007) 115, 1-161.

EFSA (European Food Safety Authority), 2007b. Opinion of the Scientific Panel on Plant protection products and their Residues on a request from the Commission on acute dietary intake assessment of pesticide residues in fruit and vegetables. 19 April 2007. The EFSA Journal (2007) 538, 1-88.

EFSA (European Food Safety Authority), 2008a. Scientific Opinion of the Panel on Plant Protection Products and their Residues (PPR Panel) on a request from the EFSA evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005. The EFSA Journal (2008) 704, 1-88.

EFSA (European Food Safety Authority), 2008b. EFSA Scientific Report, . Addendum to the reasoned opinion on the potential chronic and acute risks to consumers' health arising from proposed temporary EU MRLs according to Regulation (EC) No 396/2005 on maximum residue levels of pesticides in food and feed of plant and animal origin. 15 February 2008. The EFSA Journal 132, 1-317.

EFSA (European Food Safety Authority), 2008c. PRIMo: Pesticide Residue Intake Model. <http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_MRLteam.htm>

EFSA (European Food Safety Authority), 2009. Guidance of the Scientific Committee on the use of the benchmark dose approach in risk assessment. 26 May 2009. The EFSA Journal (2009) 1150, 1-72.

Elia, M., Moretto, A. and Visentin, S., 2006. SAFEFOODNET: An ongoing project on chemical food safety: Network for enlarging Europe. In: Chemicals as intentional and accidental global environmental threats. Simeonov L, Chirila E (eds.), Springer, pp. 237-246.

EPA (U.S. Environmental Protection Agency), 2000. Assigning values to non- detected/non-quantified pesticide residues in human-health food exposure assessments. March 23, 2000 <http://www.epa.gov/pesticides/trac/science/trac3b012.pdf>

EPA (U.S. Environmental Protection Agency), 2006. 1,2,4-Triazole, triazole Alanine, Triazole Acetic Acid: Human Health Aggregate Risk Assessment in Support of Reregistration and Registration Actions for Triazole-derivative Fungicide Compounds. Washington, DC. www.epa.gov/opprd001/factsheets/tetraHHRA.pdf

FAO/WHO (Food and Agriculture Organization/World Health Organization), 1990. Pesticide Residues in Food – 1990 evaluations. Toxicology.World Health Organisation. WHO/PCS91.47,1991, nos 802-816 on INCHEM.

FAO/WHO, (Food and Agriculture Organization/World Health Organization), 1995. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment Groups. FAO Plant Production and Protection Paper, 133, 1996.

FAO/WHO, (Food and Agriculture Organization/World Health Organization), 1997. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. FAO Plant Production and Protection Paper, 145, 1998.

FAO/WHO (Food and Agriculture Organization/World Health Organization), 1998. Pesticide Residues in Food – 1998: part II Toxicological/ Joint Meeting of the FAO Panel of Experts on Pesticides Residues in Food and the Environment and the WHO Core Assessment Group, WHO/PC/S99.18.

FAO/WHO (Food and Agriculture Organization/World Health Organization), 1999. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. FAO Plant Production and Protection Paper, 148, 1999.

FAO/WHO (Food and Agriculture Organization/World Health Organization), 2002. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. FAO Plant Production and Protection Paper, 172, 2002.

FAO/WHO, (Food and Agriculture Organization/World Health Organization), 2004. Pesticide residues in food – 2004: Toxicological evaluations : part II / Joint Meeting of the FAO Panel of Experts on Pesticides Residues in Food and the Environment and the WHO Core Assessment Group, Rome, Italy 20–29 September 2004, WHO/PCS/06.1.

FAO/WHO, (Food and Agriculture Organization/World Health Organisation), 2007. Pesticide Residues in Food – 2007. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residue in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues. Plant Production and Protection Paper 191 (Rome: WHO, FAO).

FAO/WHO, (Food and Agriculture Organization/World Health Organization), 2008. Pesticide residues in food – 2008: Report of the Joint Meeting of the FAO Panel of Experts on Pesticides Residues in Food and the Environment and the WHO Core Assessment Group, Plant Production and Protection Paper 193 (Rome, 2009).

Goetz, A.K., Ren, H., Schmid, J.E., Blystone, C.R., Thillainadarajah, I., Best, D.S., Nichols, H.P., Strader, L.F., Wolf, D.C., Narotsky, M.G., Rockett, J.C. and Dix, D.J., 2007. Disruption of testosterone homeostasis as a mode of Action for the reproductive toxicity of triazole fungicides in the male rat. Toxicological sciences 95(1), 227–239.

Lopez, A., Rueda, C., Armentia, A., Rodriguez, M., Cuervo and Ociuo, L.A., 2003. Validation and sensitivity analysis of a probabilistic model for dietary intake assessment to pesticide residues with a Basque Country duplicate diet study. Food additive and Contaminants 20 (Suppl. 1), 87-101

Madelin, R., 2004. The importance of scientific advice in the Community decision makingprocess. Opening address to the Inaugural Joint Meeting of the members of the Non-Food Scientific Committees. Directorate General for Health and Consumer Protection, European Commission, Brussels.

Menegola, E., Broccia, M.L., Di Renzo, F., Massa, V. and Giavini, E., 2005. Study on the common teratogenic pathway elicited by the fungicides triazole-derivatives. Toxicology in Vitro 19, 737–748.

Menegola, E., Broccia, M.L., Di Renzo, F., Massa, V. and Giavini, E., 2006. Postulated pathogenic pathway in triazole fungicide induced dysmorphogenic effects. Reproductive Toxicology 22, 186-195.

Nichele, V., Andrieu, E., Boizot, C., Caillavet F. and Darmon, N., 2005. La consommation d'aliments et de nutriments en France – Evolution 1969-2001. Institut National de la Recherche Argonomique – CORELA, Doc 05-07. Yvry-Sur-Seine, France.

Nusser, S.M., Carriquiry, A.L., Dodd, K.W. and Fuller, W.A., 1996. A semiparametric transformation approach to estimating usual daily intake distributions. Journal of the American Statistical Association 91, 1440-1449.

Nusser S.M., Fuller, W.A. and Guenther, P.M., 1997. Estimating usual dietary intake distributions: adjusting for measurement error and nonnormality in 24-hour food intake data. In: Survey Measurement and Process Quality. Lyberg, L., Biemer P., Collins, M., DeLeeuw, E., Dippo, C., Schwartz, N. and Trewin, D. (eds.). New York, Wiley. pp. 689-709.

OECD (Organization for Economic Cooperation and Development), 2001. OECD guideline for testing of chemicals. Guideline 414: Prenatal development toxicity study.

Ruprich, J., Dofkova, M., Rehurkova, I., Slamenikova, E. and Resova, D., 2006. Individual food consumption - the national study SISP04. Prague, CHFCH NIPH.<http://www.chpr.szu.cz/spotrebapotravin.htm>

Rockett, J.C., Narotsky, M.G., Thompson, K.E., Thillainadarajah, I., Blystone, C.R., Goetz, A.K., Ren, H., Best, D.S., Murrell, R.N., Nichols, H.P., Schmid, J.E., Wolf, D.C. and Dix, D.J., 2006. Effect of conazole fungicides on reproductive development in the female rat. Reproductive Toxicology 22, 647–658.

Ross, A.J., Moore, T. and Leavitt, S.A. 2009. In vivo mutagenicity of conazole fungicides correlates with tumorigenicity. Mutagenesis, 24(2), 149-152.

Slob, W. 2006. Probabilistic dietary exposure assessment taking into account variability in both amount and frequency of consumption. Food and Chemical Toxicology 44, 933-951.

Taxvig, C., Haas, U., Axelstad, M., Dalgaard, M., Boberg, J., Andersen, H.R. and Vingaard, A.M., 2007. Endocrine-disrupting activities in vivo of the fungicides tebuconazole and epoxiconazole. Toxicological sciences 100 (20), 464-473.

Tully, D.B., Bao, W., Goetz, A.K., Blystone, C.R., Ren, H., Schmid, J.E., Strader, L.F., Wood, C.R., Best, D.S., Narotsky, M.G., Wolf, D.C., Rockett, J.C. and Dix, D.J. 2006. Gene expression profiling in liver and testis of rats to characterize the toxicity of triazole fungicides. Toxicology and Applied Pharmacology 215, 260–273.

Turrini, A., Saba, A., Perrone, D., Cialfa, E. and D'Amicis, A., 2001. Food consumption patterns in Italy: the INN-CA Study 1994-1996. European Journal of Clinical Nutrition 55, 571-588.

van Dooren, M.M.H., Boeijen, I., van Klaveren, J.D. and van Donkersgoed, G., 1995. Conversie van consumeerbare voedingsmiddelen naar primaire agrarische produkten (Conversion of consumed foods into raw agricultural commodities). Wageningen, RIKILT-DLO: 22.

van Klaveren, J.D., van Donkersgoed, G., van der Voet, H., Stephenson, C. and Boon, P.E., 2009. Cumulative exposure assessment of triazole pesticides. RIKILT Report 2009.008.

Volatier, J.-L., 2000. Enquête INCA individuelle et nationale sur les consommations alimentaires. Tech & Doc, Paris, Agence Française de Sécurité Sanitaire des Aliments (AFSSA).

Ward, W.O., Delker, D.A., Hester, S.D., Thai, S.-F., Wolf, D.C., Allen, J.W. and Nesnow, S., 2006.Transcriptional profiles in liver from mice treated with hepatotumorigenic and non-hepatotumorigenic triazole conazole fungicides: propiconazole, triadimefon, and myclobutanil. Toxicologic Pathology, 34:7, 863 - 878

Wolf, D.C., Allen, J. W., George, M.H., Hester, S.D., Guobin Sun, Moore, T., Thai, S.-F., Delker, D.A., Winkfield., E., Leavitt, S., Nelson, G., Roop, B.C., Jones, C., Thibodeaux, J., Nesnow, S. 2006. Toxicity Profiles in Rats Treated with Tumorigenic and Nontumorigenic Triazole Conazole Fungicides: Propiconazole, Triadimefon, and Myclobutanil. Toxicologic Pathology, 34:895–902.

WHO (World Health Organization), 1997a. Guidelines for predicting dietary intake of pesticide residues (WHO/FSF/FOS/97.7). Geneva: World Health Organization.

WHO (World Health Organization), 1997b. Food consumption and exposure assessment of chemicals. Report of a FAO/WHO consultation. Geneva. Switzerland Guidelines for pr

WHO (World Health Organization), 2003. GEMS/Food Regional Diets, Global Environment Monitoring System/Food Contamination Monitoring and Assessment Programme, Food Safety Department, World Health Organisation (WHO), Geneva, Switzerland.

WHO (World Health Organization), 2006. GEMS/Food Consumption Cluster Diets, Global Environmental Monitoring System – Food Contamination Monitoring and Assessment Programme, Food Safety Department, World Health Organisation (WHO), Geneva, Switzerland.

WHO (World Health Organization), 2008a. DIETARY EXPOSURE ASSESSMENT OF CHEMICALS IN FOOD Report of a Joint FAO/WHO Consultation Annapolis, Maryland, USA 2–6 May 2005, <http://whqlibdoc.who.int/publications/2008/9789241597470_eng.pdf>

WHO (World Health Organization), 2008b. International Programme on Chemical Safety (IPCS) Draft IPCS Framework and Sample Case Study. Combined exposure to Multiple Chemicals. February 25th/08.

Zarn, J.A., Brüschweiler, B.J. and Schlatter, J.R., 2003. Azole fungicides affect mammalian steroidogenesis by inhibiting sterol 14α-demethylase and aromatase. Environmental Health Perspectives, 111,255–261.

ABBREVIATIONS

adHI: Adjusted Hazard Index

ADI : Acceptable Daily Intake

AGD: Ano-genital distance

ARfD : Acute Reference Dose

BMD: Benchmark Dose

CAG: Cumulative Assessment Group

CRI: Cumulative Risk Index

CSAF: Chemical Specific Adjustment Factor

DAR: Draft Assessment Report

FBS: Food Balance Sheet

HI: Hazard Index

HQ: Hazard Quotient

HR: Highest residue

IC: Index Compound

I(N)EDI: International (National) Estimated Daily Intake

I(N)ESTI: International (National) Estimates of Short Term Intake

LOAEL: Lowest Observed Adverse Effect Level

LOD: Limit Of Detection

LOQ: Limit of Quantification

LOR: Limit Of Reporting

LP: Large Portion

MCRA: Monte Carlo Risk Assessment

MOA: Mode Of Action

MOE: Margin Of Exposure

MRL: Maximum Residue Level

ND: Non-Detect

NOAEL: No Observed Adverse Effect Level

PBTK modeling: Physiologically-Based Pharmacokinetic modeling

APPENDICES:

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APPENDIX I	**Deterministic estimations of background exposure of French consumers**
APPENDIX J	**Estimation of dietary cumulative exposure of French consumers**
APPENDIX K	**Risk assessments of dietary cumulative exposure of Dutch and French consumers**
APPENDIX L	**Evaluation of the methodology**

APPENDIX A

TRIAZOLE FUNGICIDES (LAST UPDATE: DECEMBER 2007)

FROM: FRAC CODE LIST 2:

MOA: G: sterol biosynthesis in membranes

Target site and code: G1: C14-demethylase in sterol biosynthesis (erg11/cyp51)

Group name: DMI-fungicides (DeMethylation Inhibitors) (SBI: Class I)

Chemical group: Triazoles

FRAC code: 3

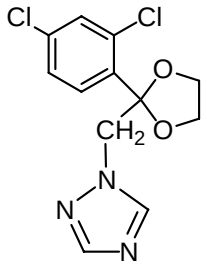
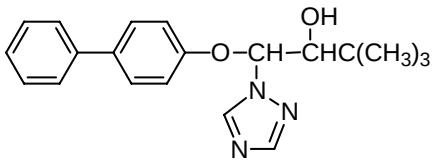
COMMON NAMES:

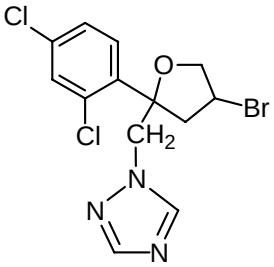
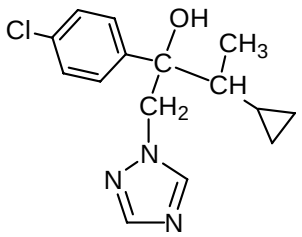
azaconazole
bitertanol
bromuconazole
cyproconazole
difenoconazole
diniconazole
epoxiconazole
etaconazole
fenbuconazole
fluquinconazole
flusilazole
flutriafol
hexaconazole
imibenconazole
ipconazole
metconazole
myclobutanil
penconazole
propiconazole
prothioconazole
simeconazole
tebuconazole
tetraconazole
triadimefon
triadimenol
triticonazole

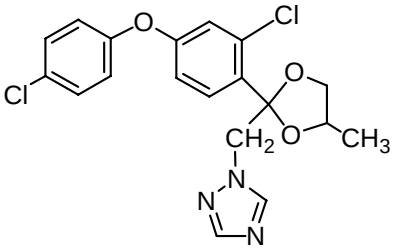
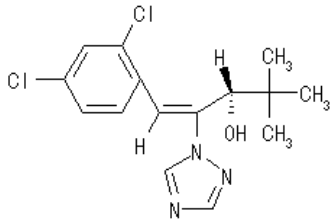
(Total: 26)

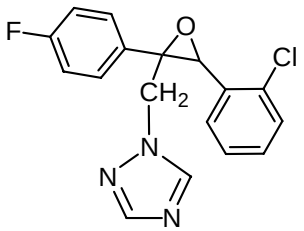
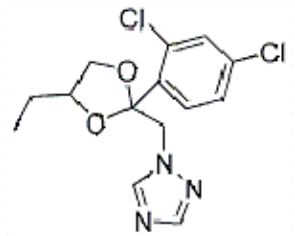
APPENDIX B

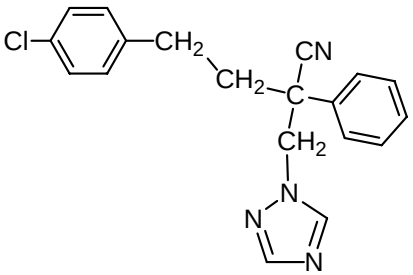
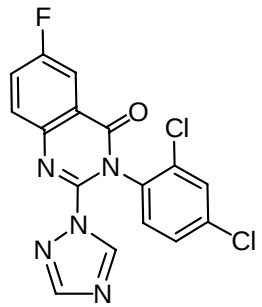
Table B1 Triazoles NOAELs for developmental, reproductive and hepatic toxicity (by April 2009)

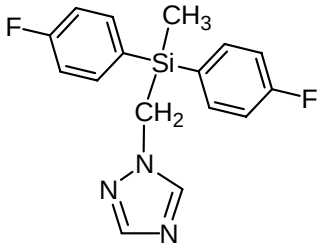
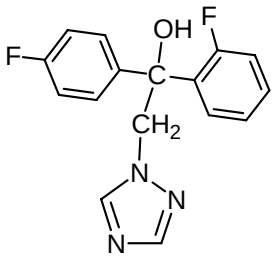
Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Azaconazole CAS No. 60207-31-0 				Withdrawn 2003 No data available Wood preservative
Bitertanol CAS No. 70585-36-3 	Rat developmental –maternal and developmental NOAEL 10 mg/kg bw/d. Malformations in rat and rabbit, evidence of adverse effects in the absence of overt maternal toxicity in rats. NOAEL for cranio-facial malformations in rat 30 mg/kg bw/day	Parental and foetal NOAEL 10 mg/kg bw/d Evidence of reduced survival and reduced pup/litter weight in rat multigeneration study.	NOAEL 0.1 mg/kg bw/d in 1-and 2-year dog study. Histopathological changes in adrenals. NOAEL 25.5 mg/kg bw/d in 2-year rat study for liver effects (increased liver weight, increased activity of serum enzymes ALP, AST)	Decision for non inclusion 5 Dec 2008 (voluntarily withdrawn) DAR

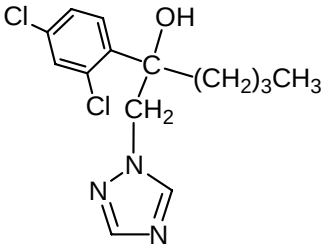
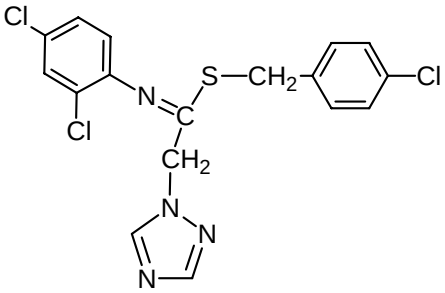
Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Bromuconazole CAS No. 116255-48-2 	Developmental NOAEL 10 mg/kg bw/d (ossification delay, supplementary cervical ribs at 70 mg/kg, which is maternal NOAEL)	NOAEL parental and foetal 1.3 mg/kg bw/d No reproductive toxicity – NOAEL 141 mg/kg bw/d (highest dose tested)	NOAEL 1 mg/kg bw/d in 2-year rat study based on hepatotoxicity (periacinar hepatocyte vacuolation, clear increase of cell foci); NOAEL for liver tumours 43.3 mg/kg bw/d	Decision for non inclusion 3 Nov 2008 (voluntarily withdrawn) DAR
Cyproconazole CAS No.94361-06-5 	NOAEL maternal, developmental, offspring in rat and rabbit 2 mg/kg bw/d Serious malformations at doses from 20 mg/kg bw/d Hydrocephalus and cleft palate in all rat studies	NOAEL 20 ppm = 1.4 mg/kg bw/d (male) based on increased liver weight, liver fatty change; 1.8 mg/kg bw/d (female) slightly increased pre-/peri and post natal losses No effect on rat fertility in 2-generation study	NOAEL 2 mg/kg bw/d in rat and mouse long-term studies – hepatotoxicity (increased relative liver weight, increased incidence of hepatocellular hypertrophy, decreased bilirubin, increased γ-GT, ALT, AST and cholesterol levels	Decision for non inclusion 5 Dec 2008 (voluntarily withdrawn) DAR

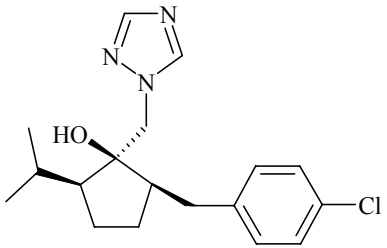
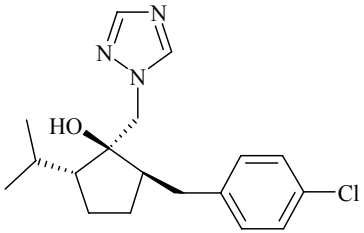
Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Difenoconazole CAS No. 119446-68-3 	Foetal NOAEL 100 mg/kg based on skeletal variations in rats. No evidence of embryotoxic, foetotoxic or teratogenic potential at doses up to 200 mg/kg day in rats and up to 75 mg/kg/day in rabbits (both the HDT)	NOAEL 17.3 mg/kg bw d based on body weight and food consumption in 2-generation study. No effect on reproduction.	NOAEL 1 mg/kg bw/d in rat 2-year study – hepatotoxicity (increased incidence and severity of hepatocellular hypertrophy)	Annex I inclusion. 1 July 2008 DAR
Diniconazole M CAS No. 83657-18-5 	Developmental NOAEL – rat, oral: 5 mg/kg bw/day Rat, oral: embryo/foetotoxicity (lower implantation efficiency, early resorptions) and skeletal variations (cervical and 14th ribs, bifid centra of thoracic vertebrae) below maternal toxic dose; NOAEL for teratogenicity in rat 80 mg/kg bw/day – external (cleft palate and minor microcephaly) and skeletal anomalies (maxillo-mandibular synostosis) at maternally toxic dose.	NOAEL parental and foetal 100 ppm (7.3 mg/kg bw/d for male and 8.6 mg/kg bw/d for female) based on liver effects NOAEL reproduction 1000 ppm (74 mg/kg bw/d for male and 87 mg/kg bw/d for female) (highest dose tested) No adverse effects on reproduction.	NOAEL 5 mg/kg bw/d in rat 2-year study – hepatotoxicity (increased incidence and severity of hepatocellular hypertrophy in both sexes)	Decision for non inclusion 18 Sept 2008 DAR Diniconazole M isomer was supported

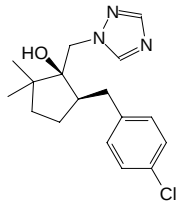
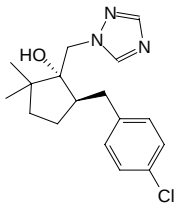
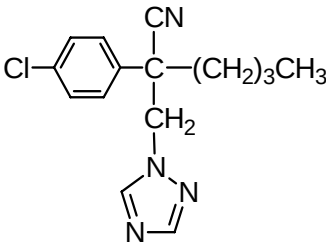
Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Epoxiconazole CAS No. 106325-08-0 	NOAEL (developmental, maternal) rat 15 mg/kg bw/d Malformations at maternally toxic doses (cleft palates), at lower dose increased skeletal variations (additional cervical ribs) and higher placental weight:	NOAEL 2.3 mg/kg bw/d (parental, reproductive, offspring) Reproductive. Toxicity at parentally toxic doses: impaired fertility, prolonged gestation, dystocia, number of viable pups reduced, perinatal mortality increased-evidence for aromatase inhibition in vitro and in vivo	NOAEL 0.8 mg/kg bw/d in 18-month mouse study based on hepatotoxicity (increased liver weight, clinical chemistry, histology)	Annex I inclusion. 25 Nov 2008 DAR
Etaconazole CAS No. 60207-93-4 				Not approved or used in any EU country Superseded. No data avalable

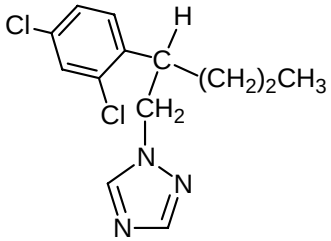
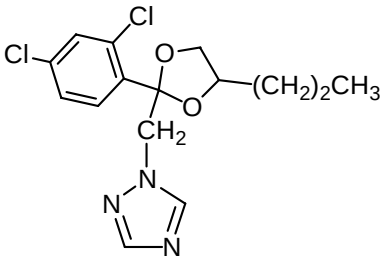
Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Fenbuconazole CAS No. 114369-43-6 	NOAEL (developmental and maternal) rat 30 mg/kg bw/d (skeletal variations/retardations seen at maternally toxic doses, increased incidence of unossified sternebrae and decreased number of implantation sites). Not teratogenic in rats or rabbits.	NOAEL for reproductive toxicity 5 mg/kg bw – reproductive effects in dams (dystocia) and foetuses (stillborns, litter loss) at a maternally and paternally toxic dose. Parental toxicity consisted of liver and thyroid effects in males, and decreased bodyweight gain in females and perturbations in the hormonal axis in pregnant animals resulting in an increase in adrenal and ovary weights, with some histopathology in the adrenal glands. There was decreased post-partum pup viability in the F1 generation, and reduced pup body weight gain in both F1 and F2 generations. Fenbuconazole did not affect the reproductive capacity of males.	NOAEL 3 mg/kg bw/d in 2-year rat study (increased liver weights with centrilobular to midzonal hepatocellular enlargement and vacuolization) NOAEL 1.3 mg/kg bw/d in 78-week mouse study (increased liver weights, hepatocellular enlargement and vacuolization)	Decision for non inclusion 5 Dec 2008 (voluntarily withdrawn) DAR
Fluquinconazole CAS No. 136426-54-5 	NOAEL (developmental and maternal) rat 2 mg/kg bw/d – Pre-implantation loss, increased number of early embryonic/foetal deaths, isolated external foetal abnormalities and some skeletal variations. Not teratogenic in rat and rabbit.	NOAEL offspring 5 ppm (0.3 mg/kg bw/d). NOAEL reproduction 50 ppm (6.8 mg/kg bw/d for male and 8.1 mg/kg bw/d for female) (highest dose tested). No adverse effects on reproduction. NOAEL parental 10 ppm (0.8 mg/kg bw/d) – clinical signs, decreased body weight gain, increased liver and kidney weights.	NOAEL 10 ppm (0.44 mg/kg bw/d for male; 0.56 mg/kg bw/d for female) – liver: increased liver weight, histopathology and tumors in females; thyroid: histopathology and follicular tumors; kidney: increased weight, chronic progressive nephropathy	Decision for non inclusion 5 Dec 2008 (voluntarily withdrawn) DAR

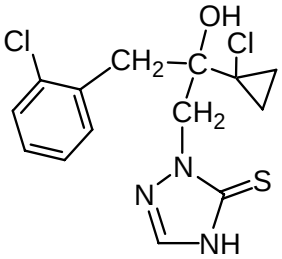
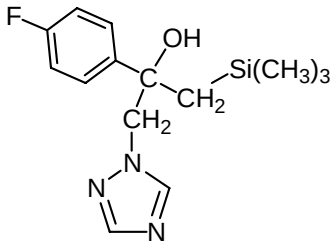
Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Flusilazole CAS No. 85509-19-9 	Developmental NOAEL 0.5 mg/kg/day (rat oral developmental toxicity study). Vaginal discharge; increased placental weight; increase in rudimentary 7th cervical ribs. NOAEL for teratogenicity in rat 50 mg/kg bw/day – at maternally toxic doses specific malformations noted were cleft palate and absent renal papillae.	NOAEL 50 ppm (2.8 – 4.6 mg/kg/day) Increased gestation length and dystocia with associated reduced pup viability and survival. Fertility parameters not affected.	NOAEL 50 ppm (2 – 2.6 mg/kg bw/d), 2-year rat study: target organs liver and bladder Testicular tumours and bladder transitional cell tumours (rat), hepatocellular tumours (mouse). NOAEL for neoplasia: 125 ppm (5.03 mg/kg/day) in male rats and 375 ppm (20.05 mg/kg/day) in female rats.	Annex 1 inclusion (temporary for 1.5 year) Review report Jan 2007 DAR
Flutriafol CAS No. 76674-21-0 	Developmental NOAEL in rat not determined –significantly increased incidences of a number of foetal skeletal parameters indicative of reduced or retarded ossification at the lowest dose level 10 mg/kg bw/d (LOAEL) No evidence of teratogenicity.	NOAEL reproduction 240 ppm (13.5 mg/kg bw/d for male and 14.4 mg/kg bw/d for female) reduced litter size. Findings associated with minor maternal bodyweight effects and mild hepatotoxicity in both sexes.	NOAEL 20 ppm (1.05 mg/kg bw/d – male – 2.6 mg/kg bw/d –female), 2-year rat study: hepatotoxicity – clinical chemistry, increased liver weight and histopathology – fatty change	Decision for non inclusion 5 Dec 2008 (voluntarily withdrawn) DAR

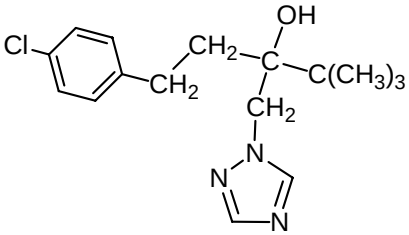
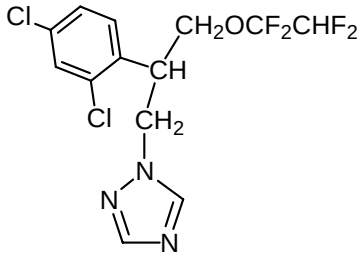
Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Hexaconazole CAS No. 79983-71-4 	Developmental NOAEL 2.5 mg/kg bw/d rat based on delayed ossification of the 7th cervical transverse process and the presence of the extra 14th rib. No structural malformations.	No adverse effects on reproduction (fertility indices, length of gestation, pre-coital interval, litter size and number of live and dead fetuses). NOAEL 20 ppm (1 mg/kg bw/d) minimal liver pathology (fatty infiltration)	NOAEL 10 ppm (0.47 mg/kg bw/d male; 0.61 mg/kg bw/d female) (decreased body weight gains in females of 7%, fatty changes in the centrilobular region of the liver of males; increased incidence of cortical vacuolation of the adrenal gland and tubular atrophy of the testes in males.	Decision for non inclusion 22 Nov 2006 No DAR available JMPR (FAO/WHO), 1990
Imibenconazole CAS No. 86598-92-7 				Not approved or used in any EU country No data avalable

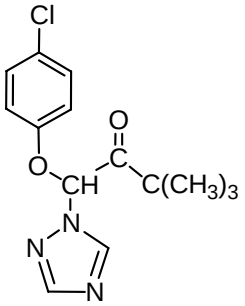
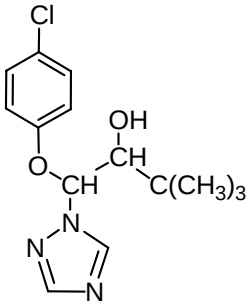
Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Ipconazole CAS No. 125225-28-7 (Mixture of diastereoisomers) 115850-69-6 (ipconazole cc, cis isomer) 115937-89-8 (ipconazole ct, trans isomer) CC diastereomer  CT diastereomer  	NOAEL developmental 10 mg/kg bw/d rat: reduced body weight, slight increase in incidence of microphthalmia and malformations of major blood vessels. (1 cleft palate and 1 cleft lip at maternal toxic dose 30 mg/kg bw/d- maternal NOAEL 10 mg/kg bw/d)	NOAEL for reproduction 300 ppm (22-26 mg/kg bw/d) the highest dose tested – no adverse effects NOAEL for offspring 100 ppm (8 mg/kg bw/d) reduced body weight gain, delayed vaginal opening	NOAEL 12.6 mg/kg bw/d in 2-year rat study (forestomach lesions, not relevant to humans) NOAEL 1.3 mg/kg bw/d in 18-month mouse study (liver histopathology) Not oncogenic in rat and mouse studies	New substance DAR not peer-reviewed Very similar structure to metconazole

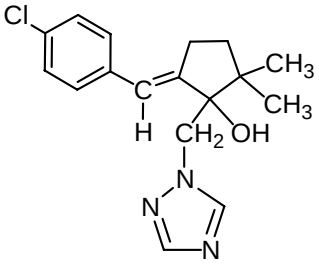
Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Metconazole CAS No. 125116-23-6 (unstated stereochemistry) (Mixture of cis- and trans- isomers**)**  cis-isomer CL 354801  trans-isomer CL 354802	Developmental NOAEL 6 mg/kg bw/d rat – increased incidence of bilateral hydroureter NOAEL maternal toxicity and foetotoxicity 24 mg/kg bw/d (maternal-decreased food consumption and bodyweight gain; embryo/foetotoxicity- increase in post-implantation loss, decrease in litter size, foetal weight)	NOAELs for parental, reproduction and offspring toxicity – 8 mg/kg bw/d; based on the absence of effect on fertility in the rat 2-generation study (modification of fertility parameters only at maternally toxic doses) The cis/trans mixture produced more maternal toxicity than the cis compound and the cis isomer produced more toxicity to offspring than the mixture.	NOAEL 100 ppm (4.6 mg/kg bw/d), 2-year rat study: target organs liver (pigment deposit and centrilobular hypertrophy of parenchymal cells) and adrenals (cortical vacuolation)	Annex 1 inclusion 21 Aug 2006 DAR
Myclobutanil CAS No. 88671-89-0 	NOAEL developmental 31 mg/kg bw/d rat- altered viability index without maternal toxicity. Increased incidence of 7th cervical rib at maternally toxic dose	Reproductive NOAEL 200 ppm (16 mg/kg/day) based on reduced numbers of females delivering litters and increased incidences of still-born pups, and decreased weight gain of offspring during lactation observed at 1000 ppm (80 mg/kg bw/d). Reproductive dysfunction evident in male rats at 1000 ppm as suggested by testicular and epididymides lesions, and prostate atrophy (80 mg/kg bw/d). These reproductive effects occurred in the presence of parental toxicity as suggested by slight body weight reduction in P2 males prior to mating and single liver cell necrosis. NOAEL systemic toxicity 200 ppm (16 mg/kg bw/d).	NOAEL 2.5 mg/kg bw/d 2-year rat study testicular atrophy NOAEL 39 mg/kg bw d for liver effects (increased relative liver weight)	Decision for non inclusion 5 Dec 2008 (voluntarily withdrawn) DAR

Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Penconazole CAS No. 66246-88-6 	NOAEL developmental 100 mg/kg bw/d rat – prenatal lethality, reduced foetal weight, increased incidence of cervical ribs. No teratogenic effects observed.	NOAELs for parental, reproduction and offspring toxicity – 30 mg/kg bw/d prolonged pregnancy/delayed parturition, increase in parturition, mortality (dams and foetuses) at parentally toxic doses	NOAEL 15 mg/kg bw/d -2-year rat study-liver effects at highest dose tested (organ weight, hepatocyte vacuolization)	Annex I inclusion. 1 Jan 2010 (voted Feb 09) DAR
Propiconazole CAS No. 60207-90-1 	NOAEL developmental 30 mg/kg bw/d rat –slight increase in cleft palate, visceral and skeletal variations at marked maternal toxic doses. The incidences of cleft palate were 0.33% at 90 mg/kg bw/d and 0.7% at 360/300 mg/kg bw/d.	NOAEL 100 ppm (5.5-15.8 mg/kg bw/d) based on histopathological liver changes. No effects on reproduction and post natal development at a dietary concentration of 500 ppm (11.5-76.2 mg/kg bw/d).	NOAEL 3.6 mg/kg bw/d, 2-year rat study hepatotoxicity	Annex 1 inclusion April 2003 Review report April 2003 DAR

Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Prothioconazole CAS No. 178928-70-6 	NOAEL developmental 80 mg/kg bw/d, rat – supernumerary rudimentary ribs	Reproductive NOAEL 95.6 mg/kg bw/d- disruption to the oestrus cycle, reduced implantation sites and litter size, increased time to insemination and duration of gestation	NOAEL 5 mg/kg bw/d, 2-year rat study targets: liver (increased weight, centrilobular hepatocellular hypertrophy with cytoplasmic change and eosinophilic/clear cell foci with cytoplasmic change); kidney (chronic progressive nephropathy)	New substance Annex I inclusion Jan 2008 DAR
Simeconazole CAS No. 149508-90-7 				No DAR available

Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Tebuconazole CAS No. 107534-96-3 	NOAEL developmental 30 mg/kg bw/d, rat Embryotoxicity and an increased incidence of malformations (mainly microphthalmia, not cranio-facial) and visceral and skeletal variations were found at 100 mg/kg bw per day and above maternally toxic doses (maternal NOAEL 10 mg/kg bw/d).	Reproductive NOAEL 72.3 mg/kg bw/d-no reproductive effects	NOAEL 55 mg/kg bw/d, 2-year rat study – liver toxicity	Annex I inclusion 19 Dec 2008 DAR
Tetraconazole CAS No. 112281-77-3 	Developmental NOAEL22.5 mg/kg bw/d, rat: hydronephrosis, hydroureter and extra ribs. Maternal NOAEL 5 mg/kg bw/d based on clinical signs and decreased body weight gain	NOAEL for reproduction, parental and offspring toxicity 3.6 mg/kg bw/d based on increased liver weights (parental), occurrence of prolonged gestation periods and dystocia (reproduction) in dams and reduced body weight gain and survival in the offspring (offspring)	NOAEL 0.4 mg/kg bw/d, 2-year rat study – liver toxicity (increased liver weights)	Proposal for restricted inclusion (Feb 2009) No qualified majority, Submitted to Council (PENDING) DAR

Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Triadimefon CAS No. 43121-43-3 	Developmental NOAEL 50 mg/kg bw/d, rat on the basis of cleft palate at 75mg/kg bw/d. Maternal NOAEL 10 mg/kg bw/d on the basis of reductions in body-weight gain.	NOAEL for reproductive toxicity 50 ppm (3.75mg/kg bw/d, on the basis of impaired reproductive performance at 1800 ppm.	NOAEL 16.4 mg/kg bw/d, 2-year rat study – liver toxicity (increased liver weights and mildly increased liver enzyme activities)	Withdrawal of support for Annex I inclusion (no dossier submitted) JMPR (FAO/WHO), 2004
Triadimenol CAS No. 55219-65-3 	Developmental NOAEL 15 mg/kg bw/d, rat: increased incidence of extra ribs and increased placental weight at maternally toxic dose. Low incidence of cleft palate at high dose level, but considered not relevant (it was range finding study and not such effects were found in the main studies).	Reproductive 6 mg/kg bw/day based on reduced fertility and decreased litter size	NOAEL 5 mg/kg bw/day 2-year rat study: hepatotoxicity (increased liver weights and related clinical chemistry changes) without any histopathological effects.	Annex I inclusion 19 Dec 2008 DAR

Name/ CAS No./Chemical structure	NOAEL for developmental toxicity	NOAEL for reproductive toxicity	NOAEL for hepatic toxicity	Source of information Remarks
Triticonazole CAS No. 131983-72-7 	Developmental NOAEL 200 mg/kg bw/d, rat, based on an apparently increase in the incidence of fetuses with an additional 14th rib or pair of ribs at all dose levels. No teratogenic effect observed at any dose level.	NOAEL for parental and reproductive toxicity 750 ppm (49.35 (male) and 48.41 (female) mg/kg bw/d), based on maternal mortality, reduced body weight and necropsy findings in adrenals, liver and ovaries in parental animals, and on significant adverse effects on reproductive parameters and on survival and growth of offspring at 5000 ppm (equivalent to 350.8-337.6 mg/kg bw/d, male and female, respectively), consistently observed across both generations.	NOAEL 750 ppm (29.4 – 38.3 mg/kg bw/d), chronic rat (99/100 weeks) based on decreased bodyweight gain and significant histopathological findings in the liver and adrenals evident at the next higher dose level.	Annex I inclusion Jan 2006 DAR

APPENDIX C

TRIAZOLES – REFERENCE VALUES USED FOR EXPOSURE ASSESSMENT (BY JUNE 2008)

Table C1 Reference values for acute exposure

Agreed by international bodies, for critical effect*			Reference value	Based on common effect – cranio-facial malformations			
Compound	**NOAEL (mg/kg bw/day)**	**LOAEL (mg/kg bw/day), species, effect**	**ARfD (mg/kg bw), SF**	**NOAEL (mg/kg bw/day)**	**LOAEL (mg/kg bw/day)**	**ARfD (mg/kg bw) SF=100**	**Reference, remarks**
Bitertanol	1.1	5 90-day dog study, clinical signs (alterations of skin and hair loss), transient weight loss, small increases in AP and ALT activities and effects on the prostate	0.01 SF 100	30	100	0.3	DAR not peer-reviewed by EFSA, proposed by RMS JMPR (FAO/WHO), 1998
Cyproconazole	2	10 maternal and developmental toxicity in rat and rabbit	0.02 SF 100	12	20	0.12	DAR not peer-reviewed, proposed by RMS
Diniconazole M	5	20 embryo/foetotoxicity in rat (early resorptions and skeletal variations-cervical and 14th ribs)	0.02 SF 250	80	300	0.8	DAR not peer-reviewed, proposed by RMS

Agreed by international bodies, for critical effect*			Reference value	Based on common effect – cranio-facial malformations			
Compound	**NOAEL (mg/kg bw/day)**	**LOAEL (mg/kg bw/day), species, effect**	**ARfD (mg/kg bw), SF**	**NOAEL (mg/kg bw/day)**	**LOAEL (mg/kg bw/day)**	**ARfD (mg/kg bw) SF=100**	**Reference, remarks**
Epoxiconasole	2.6	26 2-generation rat study (maternal, parental, reproductive and developmental toxicity)	0.03 SF 100	60	180	0.6	DAR not peer-reviewed, proposed by RMS
Flusilazole (IC)	0.5	2 developmental toxicity in rat (vaginal discharge; increased placental weight; increase in rudimentary 7th cervical ribs)	0.005 SF 100	50	250	0.5	Review report, January 2007, temporary Annex I inclusion
Propiconazole	30	90 developmental toxicity in rat (slight increase in cleft palate, visceral and skeletal variations at marked maternally toxic doses)	0.3 SF 100	30	90	0.3	Review report, April 2003, Annex 1 inclusion
Triadimefon	2	35 acute neurotoxicity, rat	0.08 SF 25	50	75	0.5	JMPR (FAO/WHO) 2004, Withdrawal Annex I

* The critical effect is the one upon which the ARfD was based

Table C2. Reference values for chronic exposure

Agreed by international bodies, for critical effect*			Reference value	Based on common effect – hepatotoxicity			
Compound	**NOAEL (mg/kg bw/day),**	**LOAEL (mg/kg bw/day), species, effect**	**ADI (mg/kg bw/day) SF**	**NOAEL (mg/kg bw/day)**	**LOAEL (mg/kg bw/day)**	**ADI (mg/kg bw/day) SF 100**	**Reference, remarks**
Bitertanol	0.1	0.3 1-and 2-year dog study, histopathological changes in adrenals.	0.001 SF 100	1 dog 25.5 rat	7.6 dog	0.01	DAR not peer-reviewed, proposed by RMS JMPR (FAO/WHO), 1998
Cyproconazole (IC)	2 (rat, mouse)	15.6 rat 13.2 mouse mouse and rat long-term study-hepatotoxicity	0.02 SF 100	2	16	0.02	DAR not peer-reviewed, proposed by RMS
Difenoconazole	1	24.1 2-year rat study, hepatotoxicity	0.01 SF 100	1	24.1	0.01	Draft review report 2008, Annex I inclusion, JMPR (FAO/WHO) 2007
Diniconazole M	5	47 2-year rat study, hepatotoxicity	0.02 SF 250	5	47	0.05	DAR not peer-reviewed, proposed by RMS
Epoxiconasole	0.8 mouse	35.5 18-month mouse study, hepatotoxicity	0.0032 SF 250	0.8 mouse		0.008	DAR not peer-reviewed, proposed by RMS
Flusilazole	0.2	0.7 1-year dog study	0.002 SF 100	<5	5	0.005 based on LOAEL 5 with SF 1000	Review report, January 2007, temporary Annex I inclusion

Agreed by international bodies, for critical effect*			Reference value	Based on common effect – hepatotoxicity			
Compound	**NOAEL (mg/kg bw/day),**	**LOAEL (mg/kg bw/day), species, effect**	**ADI (mg/kg bw/day) SF**	**NOAEL (mg/kg bw/day)**	**LOAEL (mg/kg bw/day)**	**ADI (mg/kg bw/day) SF 100**	**Reference, remarks**
Myclobutanil	2.5	9.9 2-year rat study (increased incidence of testicular atrophy)	0.025 SF 100	39	106	0.39	DAR not peer-reviewed, proposed by RMS
Propiconazole	3.6	18 2-year rat study, hepatotoxicity	0.04 SF 100	3.6	18	0.036	Review report, April 2003, Annex I inclusion
Tebuconazole	3	4.4 1-year dog study, subtle hypertrophy of adrenal zona fasciculata cells in all animals	0.03 SF 100	16	55	0.16	DAR not peer-reviewed, proposed by RMS
Triadimefon	3.4	54.6 13-week neurotoxicity study in rat	0.03 SF 100	16.4	25	0.16	JMPR (FAO/WHO) 2004, Withdrawal Annex I (not supported)
Triadimenol	4 (overall)	15 2-year dog study 54.6 13-week rat neurotoxicity study	0.01 SF 300	5	19	0.05	DAR not peer-reviewed, proposed by RMS

*The critical effect is the one upon which the ADI was based

APPENDIX D

SUMMARY OF PESTICIDE RESIDUE MONITORING DATA USED IN WORKED EXAMPLE

Table D1. Summary of pesticide residue monitoring data used in worked example (note that in deterministic tiers, only data from FR and NL were used)

Member State	Years of monitoring	Number of CAG triazoles sought in analysis[1]	Number of commodities sampled[2]	Number of samples x number of triazoles sought	Number of Samples >LOR[3]
Czech Republic	**2004-2006**	6	94	12791	30
Finland	**2003-2006**	10	57	32245	100
Italy	**2002-2004**	9	81	93194	175
Sweden	**2003-2006**	9	94	58020	205
France	**2004-2006**	11	162	80082	175
United Kingdom	**2004-2006**	9	42	37270	288
Netherlands	**2002-2007**	11	142	238496	2245

1 See Table 2 for list of compounds in CAG
2 For some MS some commodities have been finely categorised, e.g. by lettuce variety
3 The LOR (level of reporting) varies between MS, between years within a MS, and with commodity

For the Czech Republic data were collected as part of the EU coordinated monitoring and the national control programmes, both performed by the official control laboratory of the Czech Agriculture and Food Inspection Authority (CAFIA).

The data from Finland were available from the annual EU coordinated programme and the national pesticide residues monitoring program. The overall programme is carried out by the National Food Safety Authority and Customs Authority. It includes samples from farm gate, retail shops and wholesalers. Domestic (Finnish) products, products from other EU member states, and imported (third country) products are covered. Most samples are randomly collected but some are targeted to products with higher rates of pesticide occurrence.

The Italian residue data were taken from the official monitoring program which includes the EU coordinated program.

For Sweden, the data have been collected within the in EU monitoring programme according to EU regulation.

For the Netherlands, the data were taken from the EU coordinated programme, performed by the Dutch Food and Consumer Product Safety Authority (VWA), and from monitoring programmes from vegetable auctions and retailers (pers comm. van Klaveren, 2009).

The French data analyses were performed by the Direction Générale de la Concurrence, de la Consommation et de la Repression de Fraude (DGCCRF) of the French department on Consumers' Affairs. The provided data were from the EU coordinated programme, collected nationally, and local programmes. These various programmes may be unspecific (monitoring plans for pesticides residues in fruit and vegetables, in cereals, etc) or targeted on specific practices (e.g. organic farming) and processes (e.g. wine making).

For the United Kingdom, the data are the combined results of the UK's Pesticide Residue Committee (PRC) surveillance programme and the national School Fruit and Vegetable Scheme (A Department of Health initiative providing fruit and vegetables to primary school children) and include also the UK findings for the EU co-ordinated programme.

APPENDIX E

Table E1 Maximum Residues Levels and supervised trials data used in the worked example for the triazole CAG

Compound	RAC	MRL (mg/kg)	Residues from supervised trials (mg/kg)	Supervised Trials Median Residue (mg/kg)
Bitertanol	**Apple**	2	0.08; 0.09(2); 0.12(2); 0.15; 0.16; 0.18; 0.23; 0.24; 0.34 [a]	0.15
	Banana	3	0.06(2); 0.1; 0.24; 0.32; 0.36 [b]	0.17
	Tomato	3	0.39; 0.41; 0.48; 0.54; 0.56;0.96(2); 0.98; 2.1; 2.4 [c]	0.76
Cyproconazole	**Table grape**	0.2	Data not available	
	Lettuce	0.05	Data not available	
	Peach	0.1	Data not available	
Diniconazole	**Table grape**	0.2	Data not available	
Epoxiconazole	**Cabbage**	0.2	Data not available	
	Wheat	0.2	<0.01(2); 0.03; 0.04; <0.05(5); 0.1 [d]	0.05

Notes:
a EU DAR, March 2005;
b JMPR (FAO/WHO), 184;
c EU DAR, March 2005;
d EU DAR April 2005;
Data may not be available because the specific uses were not considered in the data sources examined: DARs for Directive 91/414/EEC inclusion assessments, JMPR (FAO/WHO) or UK evaluations
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APPENDIX F

EXTRAPOLATION OF OBSERVED RESIDUE CONCENTRATIONS IN SPECIFIC COMMODITIES TO SIMILAR COMMODITIES WHERE SPECIFIC RESIDUES NOT SOUGHT

Table F1. Overview of extrapolations used for the probabilistic exposure estimations

Compound	Commodity A in which specific residues monitored	Commodity B where residue not monitored, and results of commodity A used as estimate of residues
Tebuconazole	Pear	Apple
	Black currants	Red and white currants,blueberries, cranberries,gooseberries, rose hips,mulberries, azarole, Elderberries
	Carrots	Horse radish, parsnip, salsify,parsley root
	Tomatoes	Aubergines
	Green beans	Peas with pods (mange-tout)
Difenoconazole	Apples and pears	Medlar, quinces, loquat
	Carrots	Horse radish, parsnip, salsify,parsley root
	Lettuce	Rocket (rucola)
	Savoy cabbage	All head cabbages
	Parsley, coriander, dill	All herbs
Triadimenol	Red currants	Black and white currants,blueberries, cranberries,gooseberries, rose hips,mulberries, azarole, Elderberries
Myclobutanil	Lemon and oranges	All other citrus
	Apples	Pears, quinces, medlar, loquat
	Peaches	Apricots, nectarines
	Raspberries	Blackberries
	Cucumbers	Gherkins, courgettes
	Melons	Pumpkins, watermelons
	Carrots	Horse radish, parsnip, salsify parsley root
Bitertanol	Apples and pears	Quinces, medlar, loquat
	Courgettes and cucumbers	Gherkins
Diniconazole	Nectarines	Peaches and apricots

APPENDIX G

PROCESSING FACTORS

Table G1. Processing factors used to adjust measured residue concentration in raw agricultural commodities to reflect anticipated residues in food as eaten

Compound	Raw agricultural commodity	Process	Processing factor
Bitertanol	Banana	Peeling	0.5
	Apple	Juicing	0.11
	Apple	Sauce/puree	0.1
	Plums (including prunes)	Sauce/puree	0.6
	Plums (including prunes)	Marmalade/jam	1
	Cherry, sweet	Washing/cleaning	0.8
	Cherry, sweet	Juicing	0.2
	Cherry, sweet	Canned/conserved	0.6
	Cherry, sweet	Marmalade/jam	0.5
	Tomato	Washing/cleaning	0.8
	Tomato	Sauce/puree	2.1
	Tomato	Canned/conserved	0.4
	Tomato	Juicing	0.1
Difenoconazole	Table-grapes	Juicing	0.5
	Table-grapes	Drying	1
	Wine-grapes	Wine making	0.35
	Apple	Sauce/puree	0.14
	Apple	Juicing	0.6
	Apple	Washing/cleaning	0.8
	Olives	Oil extraction	1.4
	Tomato	Canned/conserved	0.07
	Tomato	Juicing	0.22
	Tomato	Sauce/puree	0.72
	Carrot	Juicing	0.06
	Carrot	Canned/conserved	0.06
Epoxiconazole	Barley	Brewing	0.1
	Wheat	Milling	1
	Wheat	Baking of bread	1
Flusilazole	Table grapes	Drying	1
	Table grapes	Juicing	0.3
	Wine grapes	Wine making	0.1
	Apple	Juicing	0.2
	Barley	Brewing	0.4
	Wheat	Milling	0.96
	Wheat	Baking of bread	1
Myclobutanil	Currants, black, red, white	Juicing	0.3
	Currants, black, red, white	Canned/conserved	1
	Strawberry	Canned/conserved	0.85
	Strawberry	Marmalade/jam	0.5
	Table grapes	Juicing	0.2
	Wine-grapes	Wine making	0.15
	Mandarins	Juicing	0.4
	Mandarins	Peeling	1
	Banana	Peeling	0.24

Compound	Raw agricultural commodity	Process	Processing factor
Myclobutanil	Apple	Washing/cleaning	1
	Apple	Juicing	0.13
	Apple	Sauce/puree	0.25
	Tomato	Canned/conserved	0.75
	Tomato	Juicing	0.58
	Tomato	Washing/cleaning	1
	Tomato	Sauce/puree	1.6
Propiconazole	Tea, green, black	Cooking in water	0.02
	Table-grapes	Juicing	0.5
	Plums(including prunes)	Drying	1
	Barley	Brewing	1
	Maize	Milling	1
	Maize	Oil extraction	0.6
	Peanut	Oil extraction	0.6
Tebuconazole	Table grapes	Juicing	0.05
	Wine grapes	Wine making	0.2
	Banana	Peeling	0.6
	Plums (including prunes)	Washing/cleaning	0.7
	Plums (including prunes)	Marmalade/jam	1
	Plums (including prunes)	Canned/conserved	0.7
	Plums (including prunes)	Drying	1
	Barley	Brewing	0.03
	Peanut	Oil extraction	0.14
Triadimefon	Table-grapes	Drying	1
	Table-grapes	Juicing	0.45
	Wine-grapes	Wine making	0.42
	Pineapple	Peeling	0.1
	Apple	Washing/cleaning	0.92
	Apple	Sauce/puree	0.63
	Apple	Juicing	0.63
	Tomato	Washing/cleaning	0.97
	Tomato	Sauce/puree	2.4
	Tomato	Sauce/puree	5.2
	Tomato	Sauce/puree	0.78
	Tomato	Juicing	0.59
	Tomato	Canned/conserved	0.59
	Tomato	Peeling	0.33
Triadimenol	Table-grapes	Drying	1
	Table-grapes	Juicing	0.78
	Wine-grapes	Wine making	0.5
	Pineapple	Peeling	0.1
	Apple	Washing/cleaning	0.92
	Apple	Juicing	0.63
	Apple	Sauce/puree	0.63
	Tomato	Sauce/puree	0.78
	Tomato	Peeling	0.33
	Tomato	Juicing	0.59
	Tomato	Sauce/puree	2.4
	Tomato	Washing/cleaning	0.97
	Tomato	Canned/conserved	0.59

Table G2. Sources to the processing data included into the above table

Pesticide	Commodity	Reference
Bitertanol	Apple	DAR 2005, JMPR (FAO/WHO) 1999
	Banana	JMPR (FAO/WHO) 1999
	Cherry	JMPR (FAO/WHO) 1999
	Plum	JMPR (FAO/WHO) 1999
	Tomato	DAR 2005, JMPR (FAO/WHO) 1999
Difenoconazole	Apple	DAR 2006, JMPR (FAO/WHO) 2007
Epoxiconazole	Carrot	JMPR (FAO/WHO) 2007
	Grapes	JMPR (FAO/WHO) 2007
	Olives	JMPR (FAO/WHO) 2007
	Tomato	JMPR (FAO/WHO) 2007
	Barley	DAR 2005
	Wheat	DAR 2005
Flusilazole	Apple	DAR addendum 2000 , UK internal data, JMPR (FAO/WHO) 2007
	Barley	DAR 1996, JMPR (FAO/WHO) 1993
	Grape	DAR addendum 2000 JMPR (FAO/WHO) 2007
	Soya bean	JMPR (FAO/WHO) 2007
	Wheat	DAR 1996, JMPR (FAO/WHO) 1993, JMPR (FAO/WHO) 2007
Myclobutanil	Apple	DAR 2005
	Banana	JMPR (FAO/WHO) 1997
	Blackcurrant	JMPR (FAO/WHO) 1997
	Grapes	DAR 2005, UK internal data
	Hops	JMPR (FAO/WHO) 1998
	Mandarin	JMPR (FAO/WHO) 1997
	Orange	JMPR (FAO/WHO) 1997
	Strawberry	JMPR (FAO/WHO) 1997
	Tomato	JMPR (FAO/WHO) 1997
Propiconazole	Barley	DAR addendum 2002
	Grapes	DAR 1998, JMPR (FAO/WHO) 2007
	Maize	DAR 1998
	Peanut	DAR 1998
	Plum	DAR 1998
	Sugar	DAR 1998
	Tea	DAR 1998, JMPR (FAO/WHO) 2007
	Wheat	DAR 1998, DAR addendum 1996
Tebuconazole	Banana	JMPR (FAO/WHO) 1997
	Barley	DAR 2006
	Grapes	DAR 2006, JMPR (FAO/WHO) 1997
	Peanut	JMPR (FAO/WHO) 1997
	Plum	JMPR (FAO/WHO) 1997
Triadimefon	Apple	JMPR (FAO/WHO) 2007
	Coffee	JMPR (FAO/WHO) 2007
	Grapes	JMPR (FAO/WHO) 2007
	Pineapple	JMPR (FAO/WHO) 1995, JMPR (FAO/WHO) 2007
	Tomato	JMPR (FAO/WHO) 2007
Triadimenol	Apple	JMPR (FAO/WHO) 2007

Pesticide	Commodity	Reference
	Coffee	JMPR (FAO/WHO) 2007
	Grapes	DAR year, JMPR (FAO/WHO) 2007
	Pineapple	JMPR (FAO/WHO) 1995, JMPR (FAO/WHO) 2007
	Tomato	JMPR (FAO/WHO) 2007

APPENDIX H

Table H1. Overview of food consumption data used in the probabilistic cumulative exposure assessments (van Klaveren et al., 2009)

Country	Years of survey	Age range (y)	Sample size	Number of days	Conse-cutive days	Survey method	Weighed/ estimated food weights	Comments	References
Czech Republic	**2003-4**	10-90	2177	2	No	24h recall	Estimated	Included all days and seasons	Ruprich et al., 2006
Czech Republic	**2003-4**	4-9	413	2	No	24h recall	Estimated	All days and seasons	Ruprich et al., 2006
France	**1998-9**	3-6	340	7	Yes	Dietary record	Estimated	All days and seasons	Volatier, 2000
France	**1998-9**	7-92	2150	7	Yes	Dietary record	Estimated	All days and seasons	Volatier, 2000
Italy	**1994-6**	1-17	283	7	Yes	Dietary record	Estimated	Excluded festive days	Turrini, et al., 2001
Italy	**1994-6**	18-64	1482	7	Yes	Dietary record	Estimated	Excluded festive days	Turrini, et al., 2001
Sweden	**1997-8**	17-79	1211	7	Yes	Dietary record	Estimated	All days and seasons	Becker, 1999; Becker and Pearson, 2002
Sweden	**2003**	3-13	2540	4	Yes	Dietary record	Estimated	All days, 2 seasons	Not published as far as known
The Netherlands	**1997-8**	1-97	6250	2	Yes	Dietary record	Weighed	All days and seasons	Anonymous, 1998
The Netherlands	**1997-8**	1-6	530	2	Yes	Dietary record	Weighed	Subset of survey above	Anonymous, 1998
The Netherlands	**2002-3**	8-12[a]	373	1	-	Dietary record	Weighed	All days & seasons [b]	Boon et al., 2004
UK	**1997-8**	4-18	1701	7	Yes	Dietary record	Weighed	All days and seasons	Gregory et al., 2000

(a) Age range is in months
(b) Breast-fed children were not included.

APPENDIX I

DETERMINISTIC ESTIMATIONS OF BACKGROUND EXPOSURE OF FRENCH CONSUMERS

Table I1. Combined background exposure regarding acute effects (cranio-facial toxicity) for French consumers (all population)

Compound	Average chronic exposure				
	Expressed in µg compound/kg bw/d	RPF (NOAEL) acute	Expressed in µg flusilazole eq./kg bw/d (NOAEL)	RPF (BMD5) acute	µg flusilazole eq./kg bw/d (BMD5)
Bitertanol	0.014	1.7	0.023	2.1	0.029
Cyproconazole	0.001	4.2	0.003	2.2	0.002
Diniconazole	0.000	0.6	0.000	1	0.000
Epoxiconazole	0.000	0.8	0.000	1.5	0.000
Flusilazole (IC)	0.001	1	0.001	1	0.001
Propiconazole	0.080	1.7	0.135	0.1	0.008
Triadimefon	0.006	1	0.006	1.2	0.008
Combined background exposure			**0.169**		**0.047**

Table I2. Combined background exposure regarding acute effects (cranio-facial toxicity) for French children (toddlers)

Compound	Average chronic exposure				
	Expressed in µg compound/kg bw/d	RPF (NOAEL) acute	Expressed in µg flusilazole eq./kg bw/d (NOAEL)	RPF (BMD5) acute	µg flusilazole eq./kg bw/d (BMD5)
Bitertanol	0.063	1.7	0.106	2.1	0.131
Cyproconazole	0.001	4.2	0.003	2.2	0.002
Diniconazole	0.000	0.6	0.000	1	0.000
Epoxiconazole	0.000	0.8	0.000	1.5	0.000
Flusilazole (IC)	0.000	1	0.000	1	0.000
Propiconazole	0.063	1.7	0.108	0.1	0.006
Triadimefon	0.012	1	0.012	1.2	0.015
Combined background exposure			**0.230**		**0.154**

Table I3. Combined background exposure regarding chronic effects (liver toxicity) for French consumers (all population)

Compound	Average chronic exposure		
	Expressed in µg compound/kg bw/d	RPF (NOAEL) chronic	Expressed in µg cyproconazole eq./kg bw/d (NOAEL)
Bitertanol	0.014	2.0	0.027
Cyproconazole (IC)	0.001	1.0	0.001
Difenoconazole	0.012	2.0	0.025
Diniconazole	0.000	0.4	0.000
Epoxiconazole	0.000	2.5	0.000
Flusilazole	0.001	4.0	0.004
Myclobutanil	0.059	0.05	0.003
Propiconazole	0.080	0.6	0.048
Tebuconazole	0.028	0.1	0.003
Triadimefon	0.006	0.1	0.001
Triadimenol	0.018	0.4	0.007
Combined background exposure			**0.118**

Table I4. Combined background exposure regarding chronic effects (liver toxicity) for French children (toddlers)

Compound	Average chronic exposure		
	Expressed in µg compound/kg bw/d	RPF (NOAEL) chronic	Expressed in µg cyproconazole eq./kg bw/d (NOAEL)
Bitertanol	0.063	2.0	0.125
Cyproconazole (IC)	0.001	1.0	0.001
Difenoconazole	0.067	2.0	0.133
Diniconazole	0.000	0.4	0.000
Epoxiconazole	0.000	2.5	0.000
Flusilazole	0.000	4.0	0.001
Myclobutanil	0.053	0.05	0.003
Propiconazole	0.063	0.6	0.038
Tebuconazole	0.112	0.1	0.011
Triadimefon	0.012	0.1	0.001
Triadimenol	0.060	0.4	0.024
Combined background exposure			**0.337**

APPENDIX J

ESTIMATION OF DIETARY CUMULATIVE EXPOSURE OF FRENCH CONSUMERS

SCENARIO 1 – ACTUAL ACUTE EXPOSURE

Deterministic estimations of dietary cumulative acute exposure were not made for French consumers due to the lack in the PRIMO model of French data for LP and unit size of commodities (sec. 3.3.1). However, acute exposure of French consumers were estimated by RIKILT using the probabilistic methodology

Table J1. Selected percentiles and mean level of estimated cumulative actual acute exposure of French consumers general and children populations (RPFs based on NOAEL ratios with IC)

Country	Consumer group	Age range	Percentiles of estimated acute exposure µg equivalents of flusilazole/kg bw/day					
			95	97.5	99	99.9	99.99	Mean
France	**French over 7 years**	**7 - 92**	0.1	0.4	0.8	2.8	8.5	0.033
France	**French Children**	**3 - 6**	0.3	0.8	1.7	7.5	20.3	0.078

Table J2. Selected percentiles and mean level of estimated cumulative actual acute exposure of Dutch general and children populations (RPFs based on BMD5 ratios with IC)

Country	Consumer group	Age range	Percentiles of estimated acute exposure µg equivalents of flusilazole/kg bw/day					
			95	97.5	99	99.9	99.99	Mean
France	**French over 7 years**	**7 - 92**	0.0	0.1	0.3	3.0	9.2	0.02
France	**French Children**	**3 - 6**	0.0	0.1	1.3	8.8	24.8	0.05

SCENARIO 2 - ACTUAL CHRONIC CUMULATIVE EXPOSURE

The dietary chronic cumulative exposure of different consumer groups was estimated by deterministic methodology as the average background exposure. Results for the French consumer groups are given in appendix I.

Probabilistic estimations using national monitoring results and NOAEL-derived RPFs[1] were made by RIKILT. As for the acute exposure assessments, the cumulative chronic exposures of different consumer groups were estimated respectively at the national and the European level. Also for this scenario the estimations included determination of exposure percentiles and the contributions from the top-3 commodities and the top-3 residues to the dietary intake[2]. The estimated percentiles of exposure of Dutch consumers are given in section 3.7.2. Results for French consumers expressed as µg equivalents of cyproconazole/kg bw/day are summarised in the Table J3 below.

1 Estimations using BMD-derived RPFs could not be performed as these BMDs were not determined. (see chapter 2)
2 The derived contributions from the top-3 commodities and the top-3 residues to the dietary intake are given in the appendix

Table J3. Selected percentiles and mean level of estimated cumulative chronic exposure of French consumer groups (all populations and children)

Country	Consumer group	Age range	Percentiles of estimated chronic exposure µg equivalents of cyproconazole/kg bw/day					
			95	97.5	99	99.9	99.99	Mean
France	**All population**	**7 - 92**	0.1	0.2	0.2	0.3	0.4	0.029
France	**Children**	**3 - 6**	0.1	0.2	0.4	0.5	0.6	0.058

SCENARIO 3 - ACUTE CUMULATIVE EXPOSURE ASSESSMENT - MRL-SETTING

As described in section 3.8 cumulative exposure estimations were carried out for a few selected pesticide/commodity combinations at MRL-level. The calculations were made by deterministic methodology based on identification of critical commodities and by probabilistic methodology, which could be performed directly without identification of critical commodities.

Point estimates of the acute cumulative exposure have been calculated for Dutch consumers. The results of these calculations are given in section 3.8 of the opinion. As the PRIMO model does not yet include French data for LP and unit size of the various commodities, the acute exposure was not estimated for French consumers. However, the probabilistic methodology made it possible to estimate the exposure of French consumers. The distributions of short term cumulative intakes were provided using both the NOAEL- and BMD-derived RPF methods for MRL-setting of bitertanole in apples. The results are described in the RIKILT report and presented in Tables J4-J5.

Table J4. Selected percentiles and mean level of estimated cumulative acute exposure of French consumers (Adult and children) (RPFs based on NOAEL ratios with IC) for MRL-setting of bitertanol in apple.

Commodity (MRL mg/kg)	Consumer group	Age range	Percentiles of estimated acute exposure µg equivalents of flusilazole/kg bw/day					
			95	97.5	99	99.9	99.99	Mean
Bitertanol/Apple (2 mg/kg)	**French adult**	**18 - 64**	24.8	32.4	43.0	72.7	111.9	7.0
Bitertanol/Apple (2 mg/kg)	**French children**	**3 - 6**	47.5	66.0	92.6	174.0	288.6	10.8

Table J5. Selected percentiles and mean level of estimated cumulative acute exposure French consumers (Adult and children) (RPFs based on BMD5 ratios with IC) for MRL-setting of bitertanol in apple.

Pesticide/Commodity combination	Consumer group	Age range	Percentiles of estimated acute exposure µg equivalents of flusilazole/kg bw/day					
			95	97.5	99	99.9	99.99	Mean
Bitertanol/Apple (2 mg/kg)	**French adult**	**1 - 97**	30.6	39.9	53.0	90.4	133.9	8.6
Bitertanol/Apple (2 mg/kg)	**French children**	**1 - 6**	58.5	81.4	114.5	218.7	364.3	13.4

SCENARIO 4 - CHRONIC CUMULATIVE EXPOSURE ASSESSMENT - MRL-SETTING

The deterministic cumulative exposure estimations are calculated as the sum of the actual chronic background and the contribution from the average consumption of the commodity for which the MRL is being assessed assuming the residue level in this commodity to be at the MRL-level. The calculations were also made assuming the level in the specific commodity to be at the STMR-level.

For Dutch consumers the results are based on STMR-data given in section 3.9. The MRL-based results for Dutch and French consumers are shown in the following tables, which also include results based on STMR-values for French consumers

Table J6. Potential chronic intake for each of the pesticide/commodity combinations at MRL level in Dutch general population.

Pesticide/commodity combination and STMR level	Chronic exposure		
	Expressed as µg compound/kg bw/d	RPF (NOAEL) chronic	Expressed as µg cyproconazole eq./kg bw/d
Bitertanol/apple (0.15 mg/kg)	2.36	2.0	4.73
Bitertanol/banana (0.17 mg/kg)	0.94	2.0	1.88
Bitertanol/tomato (0.76 mg/kg)	1.28	2.0	2.56
Epoxiconazole/wheat (0.05 mg/kg)	0.41	2.5	1.04

Table J7. Potential chronic intake for each of the pesticide/commodity combinations at MRL level in Dutch children population.

Pesticide/commodity combination and STMR level	Chronic exposure		
	Expressed as µg compound/kg bw/d	RPF (NOAEL) chronic	Expressed as µg cyproconazole eq./kg bw/d
Bitertanol/apple (0.15 mg/kg)	12.67	2.0	25.33
Bitertanol/banana (0.17 mg/kg)	5.11	2.0	10.22
Bitertanol/tomato (0.76 mg/kg)	1.87	2.0	3.74
Epoxiconazole/wheat (0.05 mg/kg)	0.95	2.5	2.38

Table J8. Potential chronic intake for each of the pesticide/commodity combinations at MRL level in French all population.

Pesticide/commodity combination and STMR level	Chronic exposure		
	Expressed as µg compound/kg bw/d	RPF (NOAEL) chronic	Expressed as µg cyproconazole eq./kg bw/d
Bitertanol/apple (0.15 mg/kg)	0.95	2.0	1.90
Bitertanol/banana (0.17 mg/kg)	0.75	2.0	1.49
Bitertanol/tomato (0.76 mg/kg)	1.30	2.0	2.60
Epoxiconazole/wheat (0.05 mg/kg)	0.66	2.5	1.64

Table J9. Potential chronic intake for each of the pesticide/commodity combinations at MRL level in French children population.

Pesticide/commodity combination and STMR level	Chronic exposure		
	Expressed as µg compound/kg bw/d	RPF (NOAEL) chronic	Expressed as µg cyproconazole eq./kg bw/d
Bitertanol/apple (0.15 mg/kg)	5.25	2.0	10.49
Bitertanol/banana (0.17 mg/kg)	3.88	2.0	7.75
Bitertanol/tomato (0.76 mg/kg)	2.32	2.0	4.64
Epoxiconazole/wheat (0.05 mg/kg)	0.53	2.5	1.31

Table J10. Potential chronic intake for each of the pesticide/commodity combinations at STMR level in French all population.

Pesticide/commodity combination and STMR level	Chronic exposure		
	Expressed as µg compound/kg bw/d	RPF (NOAEL) chronic	Expressed as µg cyproconazole eq./kg bw/d
Bitertanol/apple (0.15 mg/kg)	0.07	2.0	0.14
Bitertanol/banana (0.17 mg/kg)	0.04	2.0	0.08
Bitertanol/tomato (0.76 mg/kg)	0.33	2.0	0.66
Epoxiconazole/wheat (0.05 mg/kg)	0.16	2.5	0.41

Table J11. Potential chronic intake for each of the pesticide/commodity combinations at STMR level in French children population.

Pesticide/commodity combination and STMR level	Chronic exposure		
	Expressed as µg compound/kg bw/d	RPF (NOAEL) chronic	Expressed as µg cyproconazole eq./kg bw/d
Bitertanol/apple (0.15 mg/kg)	0.39	2.0	0.79
Bitertanol/banana (0.17 mg/kg)	0.22	2.0	0.44
Bitertanol/tomato (0.76 mg/kg)	0.59	2.0	1.18
Epoxiconazole/wheat (0.05 mg/kg)	0.13	2.5	0.33

Probabilistic intake estimations at STMR-level were made for the Dutch consumers. The results of these estimations are given in section 3.9.2. For French consumers the calculations were made for bitertanol/apple and epoxiconazole/wheat. The results of these calculations are summarised in Table J12 below:

Table J12. Selected percentiles and mean level of estimated cumulative chronic exposure of French consumers (RPFs based on NOAEL) for the selected pesticide/commodity combinations at STMR-level

Commodity	Consumer group	Age range	Percentiles of estimated chronic combined exposure µg equivalents of cyproconazole/kg bw/day					
			90	95	99	99,9	99.99	Mean
Bitertanol/Apple	**Adult**	**18 - 64**	0.5	0.6	0.9	1.4	1.5	0.2
Bitertanol/Apple	**Children**	**3 - 6**	1.0	1.3	1.9	2.7	2.9	0.5
Epoxiconazole/wheat	**Children**	**3 - 6**	0.8	0.9	1.2	1.5	1.5	0.5

APPENDIX K

RISK ASSESSMENTS OF DIETARY CUMULATIVE EXPOSURE OF DUTCH AND FRENCH CONSUMERS

This appendix includes the background calculations of the Hazard Index, the adjusted Hazard Index and the RPF adjusted exposures estimated by using the deterministic methodology. Risk assessments based on probabilistic estimated exposures are described in chapter 4 of the opinion and detailed information about the estimations is given in the RIKILT report

SCENARIO 1 – ACTUAL ACUTE CUMULATIVE RISK ASSESSMENT

Table K1. Summary of risk assessments of acute cumulative intake calculations of actual exposure of Dutch consumers (total population)

Compound	Critical commodity	Hazard Index	Hazard Index adjusted	Acute exposure (RPF adjusted)	
				% ARfD (flusilazole)	
				NOAEL*	BMD+
Bitertanol	Bananas	0.781	0.026	2.68	3.28
Cyproconazole	Table grapes	0.143	0.022	2.21	1.19
Diniconazole	Table grapes	0.080	0.002	0.24	0.32
Epoxiconazole	Leek	0.042	0.002	0.21	0.30
Flusilazole	Table grapes	0.523	0.006	0.59	0.58
Propiconazole	Broccoli	0.041	0.026	2.62	0.22
Triadimefon	Pine apples	0.274	0.042	4.21	5.02

* RPFs based on NOAELs
\+ RPFs based on BMDs

The exposure for each residue has been calculated as the sum of the background exposure from all residues and all food commodities plus the intake from consumption of a large portion (LP) size meal of the critical commodity, which is the commodity causing the highest individual exposure.

Table K2. Bitertanol: Max level in bananas

Dutch total population

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
		Set by international bodies	Based on common effect	NOAEL	BMD				RPF adjusted	
				IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol	in LP bananas	0.01	0.3	1.7	2.1	0.0076533	0.76533	0.0255110	0.0130106	0.0160719
	Without bananas	0.01	0.3	1.7	2.1	0.0000283	0.00283	0.0000945	0.0000482	0.0000595
Cyproconazole		0.02	0.12	4.2	2.2	0.0000374	0.00187	0.0003117	0.0001571	0.0000823
Diniconazole		0.02	0.8	0.6	1	0.0000310	0.00155	0.0000388	0.0000186	0.0000310
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000238	0.00079	0.0000397	0.0000190	0.0000357
Flusilazole		0.005	0.5	1	1	0.0000376	0.00752	0.0000752	0.0000376	0.0000376
Propiconazole		0.3	0.3	1.7	0.1	0.0000372	0.00012	0.0001240	0.0000632	0.0000037
Triadimefon		0.08	0.5	1	1.2	0.0000704	0.00088	0.0001408	0.0000704	0.0000845
Cumullative							**0.781**	**0.026**	**0.013**	**0.016**

Commodity:	**Bananas**		**%ARfD(flusilazole)**
Variability Factor:	7		**2.7** / **3.3**
LP:	260	g	
LP - Exposure:	0.0076533	mg/kg bw/day	
Monitoring:	0.00002834	mg/kg bw/day	

* RPFs based on NOAELs

+ RPFs based on BMDs

Table K3. Cyproconazole: Max level in table grapes

Dutch total population

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
		Set by international bodies	Based on common effect	NOAEL IC (flusilazole)	BMD IC (flusilazole)	mg/kg bw/day			RPF adjusted NOAEL*	RPF adjusted BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0000373	0.00373	0.0001243	0.0000634	0.0000783
Cyproconazole	In LP Table grapes	0.02	0.12	4.2	2.2	0.0025397	0.12698	0.0211640	0.0106667	0.0055873
	Without Table grapes	0.02	0.12	4.2	2.2	0.0000317	0.00158	0.0002638	0.0001330	0.0000697
Diniconazole		0.02	0.8	0.6	1	0.0000310	0.00155	0.0000388	0.0000186	0.0000310
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000238	0.00079	0.0000397	0.0000190	0.0000357
Flusilazole		0.005	0.5	1	1	0.0000376	0.00752	0.0000752	0.0000376	0.0000376
Propiconazole		0.3	0.3	1.7	0.1	0.0000372	0.00012	0.0001240	0.0000632	0.0000037
Triadimefon		0.08	0.5	1	1.2	0.0000704	0.00088	0.0001408	0.0000704	0.0000845
Cumullative							**0.143**	**0.022**	**0.011**	**0.006**

Commodity:	**Table grapes**		**%ARfD(flusilazole)**
Variability Factor:	5		**2.2** **1.2**
LP:	400	g	
LP Exposure:	0.00253968	mg/kg bw/day	
Monitoring:	0.00003166	mg/kg bw/day	

* RPFs based on NOAELs
+ RPFs based on BMDs

Table K4. Diniconazole: Max level in table grapes

Dutch total population

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
				NOAEL	BMD				RPF adjusted	
		Set by international bodies	Based on common effect	IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0000373	0.00373	0.0001243	0.0000634	0.0000783
Cyproconazole		0.02	0.12	4.2	2.2	0.0000374	0.00187	0.0003117	0.0001571	0.0000823
Diniconazole	InLP-tablegrapes	0.02	0.8	0.6	1	0.0012720	0.06360	0.0015900	0.0007632	0.0012720
	Without tablegrapes	0.02	0.8	0.6	1	0.0000252	0.00126	0.0000315	0.0000151	0.0000252
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000238	0.00079	0.0000397	0.0000190	0.0000357
Flusilazole		0.005	0.5	1	1	0.0000376	0.00752	0.0000752	0.0000376	0.0000376
Propiconazole		0.3	0.3	1.7	0.1	0.0000372	0.00012	0.0001240	0.0000632	0.0000037
Triadimefon		0.08	0.5	1	1.2	0.0000704	0.00088	0.0001408	0.0000704	0.0000845
Cumullative							**0.080**	**0.002**	**0.001**	**0.002**

			%ARfD(flusilazole)	
Commodity:	**Tablegrapes**			
Variability Factor:	5		**0.2**	**0.3**
LP:	400	g		
Exposure:	0.001272	mg/kgbw/dag		
Monitoring:	0.0000252	mg/kgbw/dag		

* RPFs based on NOAELs
\+ RPFs based on BMDs

Table K5. Epoxiconazole: Max level in leek

Dutch total population

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure	
		Set by international bodies	Based on common effect	NOAEL	BMD				RPF adjusted	
				IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0000373	0.00373	0.0001243	0.0000634	0.0000783
Cyproconazole		0.02	0.12	4.2	2.2	0.0000374	0.00187	0.0003117	0.0001571	0.0000823
Diniconazole		0.02	0.8	0.6	1	0.0000310	0.00155	0.0000388	0.0000186	0.0000310
Epoxiconazole	In LP-leek	0.03	0.6	0.8	1.5	0.0007650	0.02550	0.0012750	0.0006120	0.0011475
	Without leek	0.03	0.6	0.8	1.5	0.0000190	0.00063	0.0000316	0.0000152	0.0000285
Flusilazole		0.005	0.5	1	1	0.0000376	0.00752	0.0000752	0.0000376	0.0000376
Propiconazole		0.3	0.3	1.7	0.1	0.0000372	0.00012	0.0001240	0.0000632	0.0000037
Triadimefon		0.08	0.5	1	1.2	0.0000704	0.00088	0.0001408	0.0000704	0.0000845
Cumullative							**0.042**	**0.002**	**0.001**	**0.001**

Commodity:	**Leek**		**%ARfD(flusilazole)**
Variability Factor:	7		**0.2** **0.3**
LP:	325	g	
Exposure:	0.000765	mg/kg bw/day	
Monitoring:	0.000018968	mg/kg bw/day	

* RPFs based on NOAELs
+ RPFs based on BMDs

Table K6. Flusilazole: Max level in table grapes

Dutch total population

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
				NOAEL	BMD				RPF adjusted	
		Set by international bodies	Based on common effect	IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0000373	0.00373	0.0001243	0.0000634	0.0000783
Cyproconazole		0.02	0.12	4.2	2.2	0.0000374	0.00187	0.0003117	0.0001571	0.0000823
Diniconazole		0.02	0.8	0.6	1	0.0000310	0.00155	0.0000388	0.0000186	0.0000310
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000238	0.00079	0.0000397	0.0000190	0.0000357
Flusilazole	In LP table grapes	0.005	0.5	1	1	0.0025395	0.50790	0.0050790	0.0025395	0.0025395
	Without table grapes	0.005	0.5	1	1	0.0000310	0.00620	0.0000620	0.0000310	0.0000310
Propiconazole		0.3	0.3	1.7	0.1	0.0000372	0.00012	0.0001240	0.0000632	0.0000037
Triadimefon		0.08	0.5	1	1.2	0.0000704	0.00088	0.0001408	0.0000704	0.0000845
Cumullative							**0.523**	**0.006**	**0.003**	**0.003**
									%ARfD(flusilazole)	
									0.6	**0.6**

Commodity: **Table grapes**
Variability Factor: 5
LP: 400 g
Exposure: 0.0025395 mg/kg bw/day
Monitoring: 0.000031 mg/kg bw/day

* RPFs based on NOAELs
+ RPFs based on BMDs

Table K7. Propiconazole: Max level in broccoli

Dutch total population

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
		Set by international bodies	Based on common effect	NOAEL	BMD				RPF adjusted	
				IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0000373	0.00373	0.0001243	0.0000634	0.0000783
Cyproconazole		0.02	0.12	4.2	2.2	0.0000374	0.00187	0.0003117	0.0001571	0.0000823
Diniconazole		0.02	0.8	0.6	1	0.0000310	0.00155	0.0000388	0.0000186	0.0000310
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000238	0.00079	0.0000397	0.0000190	0.0000357
Flusilazole		0.005	0.5	1	1	0.0000376	0.00752	0.0000752	0.0000376	0.0000376
Propiconazole	In LP-broccoli	0.3	0.3	1.7	0.1	0.0074634	0.02488	0.0248780	0.0126878	0.0007463
Propiconazole	Without broccoli	0.3	0.3	1.7	0.1	0.0000350	0.00012	0.0001165	0.0000594	0.0000035
Triadimefon		0.08	0.5	1	1.2	0.0000704	0.00088	0.0001408	0.0000704	0.0000845
Cumullative							**0.041**	**0.026**	**0.013**	**0.001**
									%ARfD(flusilazole)	
									2.6	**0.22**

Commodity: **Broccoli**
Variability Factor: 5
LP: 319 g
Exposure: 0.0074634 mg/kg bw/day
Monitoring: 3.49632E-05 mg/kg bw/day
* RPFs based on NOAELs
+ RPFs based on BMDs

Table K8. Triadimefon: Max level in pine apples

Dutch total population

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
				NOAEL	BMD				RPF adjusted	
		Set by international bodies	Based on common effect	IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0000373	0.00373	0.0001243	0.0000634	0.0000783
Cyproconazole		0.02	0.12	4.2	2.2	0.0000374	0.00187	0.0003117	0.0001571	0.0000823
Diniconazole		0.02	0.8	0.6	1	0.0000310	0.00155	0.0000388	0.0000186	0.0000310
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000238	0.00079	0.0000397	0.0000190	0.0000357
Flusilazole		0.005	0.5	1	1	0.0000376	0.00752	0.0000752	0.0000376	0.0000376
Propiconazole		0.3	0.3	1.7	0.1	0.0000372	0.00012	0.0001240	0.0000632	0.0000037
Triadimefon	In LP pine apples	0.08	0.5	1	1.2	0.0206500	0.25813	0.0413000	0.0206500	0.0247800
Triadimefon	Without pine apples	0.08	0.5	1	1.2	0.0000605	0.00076	0.0001210	0.0000605	0.0000726
Cumulative							**0.274**	**0.042**	**0.0211**	**0.0251**
									%ARfD(flusilazole)	
									4.2	**5.0**

Commodity: **Pine apples**
Variability Factor: 5
LP: 345.6 g
Exposure: 0.02065 mg/kg bw/day
Monitoring: 0.00006048 mg/kg bw/day
* RPFs based on NOAELs
+ RPFs based on BMDs

Table K9. Summary of risk assessments: Acute cumulative intake calculations of actual exposure

Dutch children

Residue	Critical commodity	Hazard Index	Hazard Index adjusted	Acute exposure (RPF adjusted)	
				% ARfD (flusilazole)	
				NOAEL*	BMD+
Bitertanol	Bananas	2.812	0.094	9.63	11.84
Cyproconazole	Table grapes	0.260	0.040	4.08	2.20
Diniconazole	Table grapes	0.143	0.005	0.44	0.61
Epoxiconazole	Leek	0.083	0.004	0.43	0.65
Flusilazole	Table grapes	0.959	0.011	1.10	1.08
Propiconazole	Broccoli	0.063	0.038	3.86	0.36
Triadimefon	Table grapes	0.170	0.025	2.46	2.90

* RPFs based on NOAELs
\+ RPFs based on BMDs

The exposure for each residue has been calculated as the sum of the background exposure from all residues and all food commodities plus the intake from consumption of a large portion (LP) size meal of the critical commodity, which is the commodity causing the highest individual exposure.

Table K10. Bitertanol: Max level in bananas

Dutch children

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
		Set by international bodies	Based on common effect	NOAEL	BMD				RPF adjusted	
				IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol	in LP bananas	0.01	0.3	1.7	2.1	0.0279000	2.79000	0.0930000	0.0474300	0.0585900
	Without bananas	0.01	0.3	1.7	2.1	0.0000597	0.00597	0.0001990	0.0001015	0.0001254
Cyproconazole		0.02	0.12	4.2	2.2	0.0000456	0.00228	0.0003800	0.0001915	0.0001003
Diniconazole		0.02	0.8	0.6	1	0.0000375	0.00188	0.0000469	0.0000225	0.0000375
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000358	0.00119	0.0000597	0.0000286	0.0000537
Flusilazole		0.005	0.5	1	1	0.0000370	0.00740	0.0000740	0.0000370	0.0000370
Propiconazole		0.3	0.3	1.7	0.1	0.0000799	0.00027	0.0002663	0.0001358	0.0000080
Triadimefon		0.08	0.5	1	1.2	0.0002240	0.00280	0.0004480	0.0002240	0.0002688
Cumullative							**2.812**	**0.094**	**0.048**	**0.059**

			%ARfD(flusilazole)	
Commodity:	**Bananas**			
Variability Factor:	7		**9.6**	**11.8**
LP:	260	g		
LP - Exposure:	0.0279	mg/kg bw/day		
Monitoring:	0.0000597	mg/kg bw/day		

* RPFs based on NOAELs
+ RPFs based on BMDs

Table K11. Cyproconazole: Max level in table grapes

Dutch children

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
				NOAEL	BMD				RPF adjusted	
		Set by international bodies	Based on common effect	IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0001084	0.01084	0.0003613	0.0001843	0.0002276
Cyproconazole	In LP Table grapes	0.02	0.12	4.2	2.2	0.0046800	0.23400	0.0390000	0.0196560	0.0102960
	Without Table grapes	0.02	0.12	4.2	2.2	0.0000266	0.00133	0.0002217	0.0001117	0.0000585
Diniconazole		0.02	0.8	0.6	1	0.0000375	0.00188	0.0000469	0.0000225	0.0000375
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000358	0.00119	0.0000597	0.0000286	0.0000537
Flusilazole		0.005	0.5	1	1	0.0000370	0.00740	0.0000740	0.0000370	0.0000370
Propiconazole		0.3	0.3	1.7	0.1	0.0000799	0.00027	0.0002663	0.0001358	0.0000080
Triadimefon		0.08	0.5	1	1.2	0.0002240	0.00280	0.0004480	0.0002240	0.0002688
Cumullative							**0.260**	**0.040**	**0.020**	**0.011**
									%ARfD(flusilazole)	
									4.1	**2.2**

Commodity: **Table grapes**
Variability Factor: 5
LP: 400 g
LP Exposure: 0.00468 mg/kg bw/day
Monitoring: 0.0000266 mg/kg bw/day

* RPFs based on NOAELs
\+ RPFs based on BMDs

Table K12. Diniconazole: Max level in table grapes

Dutch Children

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
		Set by international bodies	Based on common effect	NOAEL	BMD				RPF adjusted	
				IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0001084	0.01084	0.0003613	0.0001843	0.0002276
Cyproconazole		0.02	0.12	4.2	2.2	0.0000456	0.00228	0.0003800	0.0001915	0.0001003
Diniconazole	In LP-table grapes	0.02	0.8	0.6	1	0.0023392	0.11696	0.0029240	0.0014035	0.0023392
	Without table grapes	0.02	0.8	0.6	1	0.0000185	0.00093	0.0000231	0.0000111	0.0000185
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000358	0.00119	0.0000597	0.0000286	0.0000537
Flusilazole		0.005	0.5	1	1	0.0000370	0.00740	0.0000740	0.0000370	0.0000370
Propiconazole		0.3	0.3	1.7	0.1	0.0000799	0.00027	0.0002663	0.0001358	0.0000080
Triadimefon		0.08	0.5	1	1.2	0.0002240	0.00280	0.0004480	0.0002240	0.0002688
Cumullative							**0.143**	**0.005**	**0.002**	**0.003**

			%ARfD(flusilazole)	
Commodity:	**Table grapes**			
Variability Factor:	5		**0.4**	**0.6**
LP:	400	g		
Exposure:	0.0023392	mg/kg bw/day		
Monitoring:	0.0000185	mg/kg bw/day		

* RPFs based on NOAELs
\+ RPFs based on BMDs

Table K13. Epoxiconazole: Max level in leek

Dutch Children

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
		Set by international bodies	Based on common effect	NOAEL	BMD				RPF adjusted	
				IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0001084	0.01084	0.0003613	0.0001843	0.0002276
Cyproconazole		0.02	0.12	4.2	2.2	0.0000456	0.00228	0.0003800	0.0001915	0.0001003
Diniconazole		0.02	0.8	0.6	1	0.0000375	0.00188	0.0000469	0.0000225	0.0000375
Epoxiconazole	In LP-leek	0.03	0.6	0.8	1.5	0.0016860	0.05620	0.0028100	0.0013488	0.0025290
	Without leek	0.03	0.6	0.8	1.5	0.0000304	0.00101	0.0000507	0.0000243	0.0000456
Flusilazole		0.005	0.5	1	1	0.0000370	0.00740	0.0000740	0.0000370	0.0000370
Propiconazole		0.3	0.3	1.7	0.1	0.0000799	0.00027	0.0002663	0.0001358	0.0000080
Triadimefon		0.08	0.5	1	1.2	0.0002240	0.00280	0.0004480	0.0002240	0.0002688
Cumullative							**0.083**	**0.004**	**0.002**	**0.003**

Commodity:	**Leek**		**%ARfD(flusilazole)**
Variability Factor:	7		**0.4** **0.7**
LP:	325	g	
Exposure:	0.001686	mg/kg bw/day	
Monitoring:	0.0000304	mg/kg bw/day	

* RPFs based on NOAELs
+ RPFs based on BMDs

Table K14. Flusilazole: Max level in table grapes

Dutch Children

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
		Set by international bodies	Based on common effect	NOAEL	BMD				RPF adjusted	
				IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0001084	0.01084	0.0003613	0.0001843	0.0002276
Cyproconazole		0.02	0.12	4.2	2.2	0.0000456	0.00228	0.0003800	0.0001915	0.0001003
Diniconazole		0.02	0.8	0.6	1	0.0000375	0.00188	0.0000469	0.0000225	0.0000375
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000358	0.00119	0.0000597	0.0000286	0.0000537
Flusilazole	In LP table grapes	0.005	0.5	1	1	0.0046800	0.93600	0.0093600	0.0046800	0.0046800
	Without table grapes	0.005	0.5	1	1	0.0000172	0.00343	0.0000343	0.0000172	0.0000172
Propiconazole		0.3	0.3	1.7	0.1	0.0000799	0.00027	0.0002663	0.0001358	0.0000080
Triadimefon		0.08	0.5	1	1.2	0.0002240	0.00280	0.0004480	0.0002240	0.0002688
Cumullative							**0.959**	**0.011**	**0.005**	**0.005**
									%ARfD(flusilazole)	
									1.1	**1.1**

Commodity: **Table grapes**
Variability Factor: 5
LP: 400 g
Exposure: 0.00468 mg/kg bw/day
Monitoring: 0.00001715 mg/kg bw/day

* RPFs based on NOAELs
\+ RPFs based on BMDs

Table K15. Propiconazole: Max level in broccoli

Dutch Children

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
				NOAEL	BMD				RPF adjusted	
		Set by international bodies	Based on common effect	IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0001084	0.01084	0.0003613	0.0001843	0.0002276
Cyproconazole		0.02	0.12	4.2	2.2	0.0000456	0.00228	0.0003800	0.0001915	0.0001003
Diniconazole		0.02	0.8	0.6	1	0.0000375	0.00188	0.0000469	0.0000225	0.0000375
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000358	0.00119	0.0000597	0.0000286	0.0000537
Flusilazole		0.005	0.5	1	1	0.0000370	0.00740	0.0000740	0.0000370	0.0000370
Propiconazole	In LP-broccoli	0.3	0.3	1.7	0.1	0.0108600	0.03620	0.0362000	0.0184620	0.0010860
Propiconazole	Without broccoli	0.3	0.3	1.7	0.1	0.0000738	0.00025	0.0002460	0.0001255	0.0000074
Triadimefon		0.08	0.5	1	1.2	0.0002240	0.00280	0.0004480	0.0002240	0.0002688
Cumullative							**0.063**	**0.038**	**0.019**	**0.002**

Commodity:	**Broccoli**		**%ARfD(flusilazole)**
Variability Factor:	5		**3.9**	**0.4**
LP:	319	g	
Exposure:	0.01086	mg/kg bw/day	
Monitoring:	0.0000738	mg/kg bw/day	

* RPFs based on NOAELs
\+ RPFs based on BMDs

Table K16. Triadimefon: Max level in table grapes

Dutch Children

Residue		ARfD mg/kg bw		RPF		Exposure	Hazard Index	Hazard Index adjusted	Acute exposure mg/kg bw/day	
		Set by international bodies	Based on common effect	NOAEL	BMD				RPF adjusted	
				IC (flusilazole)	IC (flusilazole)	mg/kg bw/day			NOAEL*	BMD+
Bitertanol		0.01	0.3	1.7	2.1	0.0001084	0.01084	0.0003613	0.0001843	0.0002276
Cyproconazole		0.02	0.12	4.2	2.2	0.0000456	0.00228	0.0003800	0.0001915	0.0001003
Diniconazole		0.02	0.8	0.6	1	0.0000375	0.00188	0.0000469	0.0000225	0.0000375
Epoxiconazole		0.03	0.6	0.8	1.5	0.0000358	0.00119	0.0000597	0.0000286	0.0000537
Flusilazole		0.005	0.5	1	1	0.0000370	0.00740	0.0000740	0.0000370	0.0000370
Propiconazole		0.3	0.3	1.7	0.1	0.0000799	0.00027	0.0002663	0.0001358	0.0000080
Triadimefon	In LP table grapes	0.08	0.5	1	1.2	0.0115000	0.14375	0.0230000	0.0115000	0.0138000
Triadimefon	Without table grapes	0.08	0.5	1	1.2	0.0002048	0.00256	0.0004096	0.0002048	0.0002458
Cumulative							**0.170**	**0.025**	**0.0123**	**0.0145**
									%ARfD(flusilazole)	
									2.5	**2.9**

Commodity: **Table grapes**
Variability Factor: 5
LP: 200 g
Exposure: 0.0115 mg/kg bw/day
Monitoring: 0.0002048 mg/kg bw/day

* RPFs based on NOAELs
\+ RPFs based on BMDs

SCENARIO 2 - ACTUAL CHRONIC CUMULATIVE RISK ASSESSMENT

Risk assessment of the actual chronic cumulative exposure estimated by deterministic methodology is described in section 4.2 of the opinion. Calculations of the Hazard Index, the adjusted Hazard Index and the RPF-adjusted exposures are based on the estimated chronic background exposure, which in fact is the same as the actual chronic exposure. The exposures were calculated assuming that residue levels below LOR in samples of commodities with findings are at ½LOR and at 0 in samples of commodities without findings. Risk assessments using ADI-and RPF-values for chronic exposure were made for the French and Dutch consumer groups. As BMDs were not determined (see main Opinion for details), only one set of RPF-adjusted exposures, those based on NOAELs, was estimated. The results of the calculations are summarised in the following tables:

Table K17. Risk assessment of actual cumulative chronic exposure of Dutch consumers (total population)

Residue	ADI Set by international bodies	ADI based on common effect	Actual Chronic exposure	Hazard index	Hazard Index adjusted	RPF (NOAEL) chronic	RPF-adjusted Actual Chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol	0,001	0,01	0,0000373	0,0373	0,0037	2	0,00007	0,37
Cyproconazole	0,02	0,02	0,0000374	0,0019	0,0019	1	0,00004	0,19
Difenoconazole	0,01	0,01	0,0001195	0,0120	0,0120	2	0,00024	1,20
Diniconazole	0,02	0,05	0,0000310	0,0016	0,0006	0,4	0,00001	0,06
Epoxiconazole	0,0032	0,008	0,0000238	0,0075	0,0030	2,5	0,00006	0,30
Flusilazole	0,002	0,005	0,0000376	0,0188	0,0075	4	0,00015	0,75
Myclobutanil	0,025	0,39	0,0001131	0,0045	0,0003	0,05	0,00001	0,03
Propiconazole	0,04	0,036	0,0000372	0,0009	0,0010	0,6	0,00002	0,11
Tebuconazole	0,03	0,16	0,0001392	0,0046	0,0009	0,1	0,00001	0,07
Triadimefon	0,03	0,16	0,0000704	0,0023	0,0004	0,1	0,00001	0,04
Triadimenol	0,01	0,05	0,0001350	0,0135	0,0027	0,4	0,00005	0,27
Cumulative				**0,105**	**0,034**		**0,00068**	**3,38**

Table K18. Risk assessment of actual cumulative chronic exposure of Dutch children

Residue	ADI Set by international bodies	ADI based on common effect	Actual Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted Actual Chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol	0.001	0.01	0.0001084	0.1084	0.0108	2	0.00022	1.08
Cyproconazole	0.02	0.02	0.0000456	0.0023	0.0023	1	0.00005	0.23
Difenoconazole	0.01	0.01	0.0003113	0.0311	0.0311	2	0.00062	3.11
Diniconazole	0.02	0.05	0.0000375	0.0019	0.0008	0.4	0.00002	0.08
Epoxiconazole	0.0032	0.008	0.0000358	0.0112	0.0045	2.5	0.00009	0.45
Flusilazole	0.002	0.005	0.0000370	0.0185	0.0074	4	0.00015	0.74
Myclobutanil	0.025	0.39	0.0002379	0.0095	0.0006	0.05	0.00001	0.06
Propiconazole	0.04	0.036	0.0000799	0.0020	0.0022	0.6	0.00005	0.24
Tebuconazole	0.03	0.16	0.0003488	0.0116	0.0022	0.1	0.00003	0.17
Triadimefon	0.03	0.16	0.0002240	0.0075	0.0014	0.1	0.00002	0.11
Triadimenol	0.01	0.05	0.0003785	0.0379	0.0076	0.4	0.00015	0.76
Cumulative				**0.242**	**0.071**		**0.00141**	**7.03**

Table K19. Risk assessment of actual cumulative exposure of French consumers (all population)

Residue	ADI Set by international bodies	ADI based on common effect	Actual Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted Actual Chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol	0.001	0.01	0.0000136	0.0136	0.0014	2	0.0000272	0.14
Cyproconazole	0.02	0.02	0.0000008	0.0000	0.0000	1	0.0000008	0.00
Difenoconazole	0.01	0.01	0.0000123	0.0012	0.0012	2	0.0000246	0.12
Diniconazole	0.02	0.05	0.0000000	0.0000	0.0000	0.4	0.0000000	0.00
Epoxiconazole	0.0032	0.008	0.0000000	0.0000	0.0000	2.5	0.0000000	0.00
Flusilazole	0.002	0.005	0.0000011	0.0005	0.0002	4	0.0000042	0.02
Myclobutanil	0.025	0.39	0.0000592	0.0024	0.0002	0.05	0.0000030	0.01
Propiconazole	0.04	0.036	0.0000796	0.0020	0.0022	0.6	0.0000477	0.24
Tebuconazole	0.03	0.16	0.0000280	0.0009	0.0002	0.1	0.0000028	0.01
Triadimefon	0.03	0.16	0.0000064	0.0002	0.0000	0.1	0.0000006	0.00
Triadimenol	0.01	0.05	0.0000180	0.0018	0.0004	0.4	0.0000072	0.04
Cumulative				**0.023**	**0.006**		**0.00012**	**0.59**

Table K20. Risk assessment of actual cumulative exposure of French consumers (children)

Residue	ADI Set by international bodies	ADI based on common effect	Actual Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted Actual Chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol	0.001	0.01	0.0000626	0.0626	0.0063	2	0.00013	0.63
Cyproconazole	0.02	0.02	0.0000008	0.0000	0.0000	1	0.00000	0.00
Difenoconazole	0.01	0.01	0.0000667	0.0067	0.0067	2	0.00013	0.67
Diniconazole	0.02	0.05	0.0000000	0.0000	0.0000	0.4	0.00000	0.00
Epoxiconazole	0.0032	0.008	0.0000000	0.0000	0.0000	2.5	0.00000	0.00
Flusilazole	0.002	0.005	0.0000001	0.0001	0.0000	4	0.00000	0.00
Myclobutanil	0.025	0.39	0.0000528	0.0021	0.0001	0.05	0.00000	0.01
Propiconazole	0.04	0.036	0.0000634	0.0016	0.0018	0.6	0.00004	0.19
Tebuconazole	0.03	0.16	0.0001124	0.0037	0.0007	0.1	0.00001	0.06
Triadimefon	0.03	0.16	0.0000123	0.0004	0.0001	0.1	0.00000	0.01
Triadimenol	0.01	0.05	0.0000591	0.0059	0.0012	0.4	0.00002	0.12
Cumulative				**0.083**	**0.017**		**0.00034**	**1.68**

SCENARIO 3 - ACUTE CUMULATIVE RISK ASSESSMENT - MRL-SETTING

Risk assessments of the acute cumulative exposure at MRL-level are described in section 4.3. The deterministic exposure estimations are based on identification of the "critical commodity", which in this scenario is the commodity for which the MRL is going to be assessed. The results for Dutch consumers (total population and children) are summarized in table 32 and 33 in section 4.3. No assessments based on deterministic point estimates were made for French consumers due to the lack of French data for LP and unit weights.

SCENARIO 4 - CHRONIC CUMULATIVE RISK ASSESSMENT - MRL-SETTING

Risk assessments of the chronic cumulative exposure at MRL-level are described in section 4.4 of the opinion. The deterministic point estimations were made for a limited number of pesticide/commodity combinations. For information purpose calculations were made assuming that the residue level in the selected pesticide/commodity was at the MRL-level. In accordance with PPR Panel's recommendations for this scenario calculations were also made for a few of the selected combination assuming a residue concentration in the pesticide/commodity at the STMR-level. The results for Dutch consumers are given in tables 36 and 37 in the opinion. The other results for Dutch as well as for French consumers are given in the tables below:

Table K21. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Total)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Apple (2 mg/kg)	0.001	0.01	0.00236	2.36	0.24	2	0.00473	23.6
Background				0.105	0.034		0.00067	3.4
Cumulative				**2.47**	**0.27**		**0.0054**	**27.00**

Table K22. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Total)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Banana (3 mg/kg)	0.001	0.01	0.00094	0.940	0.094	2	0.00188	9.4
Background				0.105	0.034		0.00067	3.4
Cumulative				**1.04**	**0.13**		**0.003**	**12.8**

Table K23. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Total)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Tomato (3 mg/kg)	0.001	0.01	0.0013	1.281	0.128	2	0.00256	12.8
Background				0.105	0.034		0.00067	3.4
Cumulative				**1.39**	**0.16**		**0.0032**	**16.2**

Table K24. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Total)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/table grapes (0.2 mg/kg)	0.02	0.02	0.000048	0.002	0.002	1	0.00005	0.23
Background				0.105	0.034		0.00067	3.37
Cumulative				**0.11**	**0.04**		**0.0007**	**3.60**

Table K25. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Total)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/Lettuce (0.05 mg/kg)	0.02	0.02	0.0000060	0.00030	0.00030	1	0.0000060	0.03
Background				0.105	0.034		0.00067	3.4
Cumulative				**0.105**	**0.034**		**0.00068**	**3.4**

Table K26. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Total)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/Peach (0.2 mg/kg)	0.02	0.02	0.0000056	0.00028	0.00028	1	0.0000056	0.028
Background				0.105	0.034		0.00067	3.4
Cumulative				**0.105**	**0.034**		**0.00068**	**3.4**

Table K27. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Total)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Diniconazole/table grapes (0.2 mg/kg)	0.02	0.05	0.0000459	0.0023	0.00092	0.4	0.00002	0.09
Background				0.105	0.034		0.00067	3.4
Cumulative				**0.107**	**0.035**		**0.00069**	**3.5**

Table K28. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Total)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Epoxiconazole/Cabbage (0.2 mg/kg)	0.0032	0.008	0.000042	0.013	0.0052	2.5	0.00010	0.52
Background				0.105	0.034		0.00067	3.4
Cumulative				**0.118**	**0.039**		**0.0008**	**3.9**

Table K29. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Total)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Epoxiconazole/wheat (0.2 mg/kg)	0.0032	0.008	0.00041	0.130	0.052	2.5	0.0010	5.2
Background				0.105	0.034		0.0007	3.4
Cumulative				**0.234**	**0.086**		**0.0017**	**8.6**

Table K30. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Apple (2 mg/kg)	0.001	0.01	0.0127	12.67	1.27	2	0.0253	126.7
Background				0.241	0.071		0.0014	7.0
Cumulative				**12.9**	**1.3**		**0.027**	**133.7**

Table K31. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Banana (3 mg/kg)	0.001	0.01	0.00511	5.111	0.511	2	0.0102	51.1
Background				0.241	0.071		0.0014	7.07.0
Cumulative				**5.35**	**0.58**			**58.1**

Table K32. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Tomato (3 mg/kg)	0.001	0.01	0.0019	1.872	0.187	2	0.00374	18.7
Background				0.241	0.071		0.0014	7.0
Cumulative				**2.1**	**0.3**		**0.0051**	**25.7**

Table K33. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/table grapes (0.2 mg/kg)	0.02	0.02	0.000152	0.008	0.008	1	0.00015	0.76
Background				0.241	0.071		0.0014	7.0
Cumulative				**0.249**	**0.079**		**0.0016**	**7.8**

Table K34. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/Lettuce (0.05 mg/kg)	0.02	0.02	0.000005	0.0003	0.0003	1	0.000005	0.03
Background				0.241	0.071		0.00140	7.0
Cumulative				**0.242**	**0.071**		**0.00141**	**7.0**

Table K35. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/Peach (0.2 mg/kg)	0.02	0.02	0.000016	0.0008	0.0008	1	0.000016	0.08
Background				0.241	0.071		0.00140	7.0
Cumulative				**0.242**	**0.072**		**0.00142**	**7.1**

Table K36. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Diniconazole/table grapes (0.2 mg/kg)	0.02	0.05	0.000152	0.008	0.003	0.4	0.000061	0.30
Background				0.241	0.071		0.00140	7.0
Cumulative				**0.259**	**0.074**		**0.00146**	**7.3**

Table K37. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Epoxiconazole/Cabbage (0.2 mg/kg)	0.0032	0.008	0.000063	0.020	0.008	2.5	0.00016	0.79
Background				0.241	0.071		0.00140	7.0
Cumulative				**0.261**	**0.079**		**0.00156**	**7.8**

Table K38. Chronic exposure at MRL-level for selected pesticide/commodity combinations. Dutch consumers (Children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Epoxiconazole/wheat (0.2 mg/kg)	0.0032	0.008	0.000948	0.296	0.119	2.5	0.00237	11.9
Background				0.241	0.071		0.00140	7.0
Cumulative				**0.54**	**0.19**		**0.00377**	**18.9**

Table K39. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (All population)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Apple (2 mg/kg)	0.001	0.01	0.0010	0.950	0.095	2	0.0019	9.5
Background				0.023	0.006		0.00012	0.6
Cumulative				**0.97**	**0.10**		**0.0020**	**10.1**

Table K40. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (All population)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Banana (3 mg/kg)	0.001	0.01	0.00075	0.745	0.075	2	0.00149	7.5
Background				0.023	0.006		0.00012	0.6
Cumulative				**0.77**	**0.081**		**0.0016**	**8.1**

Table K41. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (All population)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Tomato (3 mg/kg)	0.001	0.01	0.0013	1.300	0.130	2	0.00260	13.0
Background				0.023	0.006		0.00012	0.6
Cumulative				**1.32**	**0.14**		**0.0027**	**13.6**

Table K42. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (All population)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/table grapes (0.2 mg/kg)	0.02	0.02	0.000022	0.001	0.001	1	0.00002	0.11
Background				0.023	0.006		0.00012	0.59
Cumulative				**0.024**	**0.007**		**0.00014**	**0.70**

Table K43. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (All population)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/Lettuce (0.05 mg/kg)	0.02	0.02	0.000005	0.0002	0.0002	1	0.000005	0.02
Background				0.023	0.006		0.00012	0.59
Cumulative				**0.023**	**0.006**		**0.00012**	**0.61**

Table K44. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (All population)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/Peach (0.2 mg/kg)	0.02	0.02	0.000014	0.0007	0.0007	1	0.000014	0.07
Background				0.023	0.006		0.00012	0.59
Cumulative				**0.023**	**0.006**		**0.00013**	**0.66**

Table K45. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (All population)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Diniconazole/table grapes (0.2 mg/kg)	0.02	0.05	0.0000215	0.001	0.00043	0.4	0.000009	0.04
Background				0.023	0.006		0.00012	0.59
Cumulative				**0.024**	**0.006**		**0.00013**	**0.63**

Table K46. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (All population)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Epoxiconazole/Cabbage (0.2 mg/kg)	0.0032	0.008	0.0000094	0.0029	0.0012	2.5	0.000023	0.12
Background				0.0230	0.006		0.00012	0.59
Cumulative				**0.026**	**0.007**		**0.00014**	**0.71**

Table K47. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (All population)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Epoxiconazole/wheat (0.2 mg/kg)	0.0032	0.008	0.00066	0.206	0.082	2.5	0.00164	8.22
Background				0.023	0.006		0.00012	0.59
Cumulative				**0.229**	**0.088**		**0.00176**	**8.8**

Table K48. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Apple (2 mg/kg)	0.001	0.01	0.0052	5.25	0.52	2	0.01049	52.5
Background				0.083	0.017		0.00034	1.7
Cumulative				**5.3**	**0.5**		**0.01083**	**54.1**

Table K49. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Banana (3 mg/kg)	0.001	0.01	0.00388	3.877	0.388	2	0.00775	38.8
Background				0.083	0.017		0.00034	1.7
Cumulative				**3.96**	**0.41**		**0.0081**	**40.5**

Table K50. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Bitertanol/Tomato (3 mg/kg)	0.001	0.01	0.0023	2.32	0.232	2	0.00464	23.2
Background				0.083	0.017		0.00034	1.7
Cumulative				**2.40**	**0.05**		**0.0050**	**24.9**

Table K51. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/table grapes (0.2 mg/kg)	0.02	0.02	0.0000042	0.00021	0.00021	1	0.0000042	0.02
Background				0.083	0.017		0.00034	1.68
Cumulative				**0.083**	**0.017**		**0.00034**	**1.7**

Table 52. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/Lettuce (0.05 mg/kg)	0.02	0.02	0.000005	0.0002	0.0002	1	0.000005	0.02
Background				0.083	0.017		0.00034	1.68
Cumulative				**0.083**	**0.017**		**0.00035**	**1.7**

Table K53. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Cyproconazole/Peach (0.2 mg/kg)	0.02	0.02	0.0000010	0.0001	0.0001	1	0.000001	0.01
Background				0.083	0.017		0.00034	1.68
Cumulative				**0.083**	**0.017**		**0.00034**	**1.7**

Table K54. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Diniconazole/table grapes (0.2 mg/kg)	0.02	0.05	0.000042	0.002	0.001	0.4	0.000017	0.08
Background				0.083	0.017		0.00034	1.68
Cumulative				**0.085**	**0.018**		**0.00036**	**1.8**

Table K55. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Epoxiconazole/Cabbage (0.2 mg/kg)	0.0032	0.008	0.000017	0.0053	0.0021	2.5	0.000042	0.21
Background				0.083	0.017		0.00034	1.68
Cumulative				**0.088**	**0.019**		**0.00038**	**1.9**

Table K56. Chronic exposure at MRL-level for selected pesticide/commodity combinations. French consumers (children)

Residue/commodity (MRL-value)	ADI set by international bodies	ADI based on common effect	Chronic exposure	Hazard index	Hazard index adjusted	RPF (NOAEL) chronic	RPF-adjusted chronic exposure	
	mg/kg bw/day	mg/kg bw/day	mg/kg bw/day			IC (cyproconazole)	mg/kg bw/day	% ADI (Cyproconazole)
Epoxiconazole/wheat (0.2 mg/kg)	0.0032	0.008	0.000525	0.164	0.066	2.5	0.00131	6.56
Background				0.083	0.017		0.00034	1.68
Cumulative				**0.247**	**0.083**		**0.00165**	**8.2**

Table K57. Risk characterisation of MRL-setting (using STMR-values) for selected pesticide/commodity combinations based on deterministic estimations of the cumulative chronic exposure of French consumers.

Residue	Commodity	Tier A-1	Tier B-1	Tier C-1	
				RPF-adjusted exposures (NOAEL)	
		Hazard index	Hazard index adjusted	µg cyproconazole eqv/kg bw/day	% ADI for liver effect (cyproconazole)
Bitertanol	**Apple**	0.09	0.01	0.26	1.3
	Banana	0.06	0.01	0.20	1.0
	Tomato	0.35	0.04	0.78	3.9
Epoxiconazole	**Wheat**	0.07	0.03	0.5	2.6

Table K58. Risk characterisation of MRL-setting (using STMR-values) for selected pesticide/commodity combinations based on deterministic estimations of the cumulative chronic exposure of French children.

Residue	Commodity	Tier A-1	Tier B-1	Tier C-1	
				RPF-adjusted exposures (NOAEL)	
		Hazard index	Hazard index adjusted	µg cyproconazole eqv/kg bw/day	% ADI for liver effects (cyproconazole)
Bitertanol	**Apple**	0.48	0.06	1.12	5.6
	Banana	0.30	0.04	0.78	3.9
	Tomato	0.67	0.08	1.51	7.6
Epoxiconazole	**Wheat**	0.12	0.03	0.7	3.3

USE OF PROCESSING FACTORS

The use of processing factors is another way to refine the exposure estimations (see chapter 1 and sec. 3.2). In this exercise, RIKILT has among others supplied the processing factors (see appendix G) for bitertanol in apple, banana and tomato, which are summarised in the table below:

Table K59 Processing factors for bitertanol in selected commodities

Raw agricultural commodity	Processing type	Processing factor
Apple	Juicing	0.11
	Sauce/puree	0.1
Banana	Peeling	0.5
Tomato	Washing/cleaning	0.8
	Sauce/puree	2.1
	Canned/conserved	0.4
	Juicing	0.1

Processing factors depend on the chemical characteristic of the pesticide, the commodity and the processing type. Unfortunately, there was no information available for this exercise about the distribution of the consumption of the raw agricultural commodity on the different processed products. It is therefore not possible to make a reasonable decision on which processing factors to be used for the deterministic exposure estimations. However, in order to illustrate the methodology the chronic cumulative risk assessments at MRL-level were recalculated for apple using a processing factor of 0.8 - which RIKILT used as the processing factor for difenoconazole for washing/cleaning of apples – and for banana and tomato using 0.5 and 0.8 respectively, as processing factors. The results are summarised in the table below.

Table K60. Summary of risk assessments of chronic cumulative exposures for bitertanol in selected commodities. Chronic cumulative exposures estimated using processing factors

Commodity	Consumer group	Hazard index	Hazard index adjusted	RPF-adjusted (NOAEL) chronic exposure	
				µg cyproconazole eqv/kg bw/day	% ADI (cyproconazole)
Apple	NL general	2.0	0.22	4.45	22.3
	NL children	10.4	1.1	21.67	108.3
	Fr. all population	0.8	0.08	1.6	8.2
	Fr. toddlers	4.3	0.44	8.73	43.6
Banana	NL general	0.6	0.08	1.61	8.1
	NL children	2.8	0.3	6.51	32.6
	Fr. all population	0.4	0.04	8.63	4.3
	Fr. toddlers	2.0	0.2	4.21	21.1
Tomato	NL general	1.1	0.14	2.72	13.6
	NL children	1.7	0.2	4.40	22.0
	Fr. all population	1.1	0.11	2.20	11.0
	Fr. toddlers	1.9	0.2	4.05	20.3

APPENDIX L

EVALUATION OF THE METHODOLOGY

Risk assessment based on adjusted Hazard Index and Relative Potency Factor

Risk assessment based on adjusted Hazard Index and Relative Potency Factors are described as different tiers in the proposed methodology for risk assessment of dietary cumulative exposure to pesticides. However, if the same safety factors are used for setting the RVs (for common effect) of the individual pesticides (SFIC = SF1 = SF2 = ... = SFn), risk assessments based on the adjusted Hazard Index are exactly the same as risk assessments based on RPFs assuming that both the RVs and RPFs are based either on BMDs or on NOAELs. This is illustrated by the following calculations:

Adjusted hazard index:

The adjusted hazard index (ad-HI) is found by summing the adjusted hazard quotients (ad-HQ) for each of the pesticides belonging to the selected Cumulative Assessment Group (CAG):

The ad-HQ for each of the pesticides is found by dividing the dietary exposure (E) by the reference value (RV), ADI or ARfD for common effect for the particular (n) pesticide:

(1) $$ad\text{-}HQ_n = \frac{E_n}{RV_n}$$

The ad-HI for the cumulative exposure is the found by:

(2) $$ad\text{-}HI = \frac{E_1}{RV_1} + \frac{E_2}{RV_2} + \frac{E_3}{RV_3} + \ldots\ldots\ldots + \frac{E_n}{RV_n}$$

However, the RV is based on the NOAEL or BMD value divided by a certain safety factor (SF) typically 10*10 = 100:

(3) $$RV_n = \frac{BMD_n}{SF_n}$$

Thus, the ad-HI can be expressed as:

(4) $$ad\text{-}HI = E_1 * \frac{SF_1}{BMD_1} + E_2 * \frac{SF_2}{BMD_2} + E_3 * \frac{SF_3}{BMD_3} + \ldots + E_n * \frac{SF_n}{BMD_n}$$

For the same safety factor (SF = SF1 = SF2 = ... = SFn), this is equal to:

(5) $$ad\text{-}HI = SF * \left(\frac{E_1}{BMD_1} + \frac{E_2}{BMD_2} + \frac{E_3}{BMD_3} + \ldots + \frac{E_n}{BMD_n}\right)$$

(6) $$ad\text{-}HI = SF^* \sum \frac{E_n}{BMD_n}$$

[A similar equation is derived when the NOAELs are used in stead of BMDs.]

Relative Potency Factors

The relative potency factors are calculated for each of the pesticides of the CAG as the ratio between the BMD (or NOAEL) values of the index compound (BMDIC) and of the individual pesticide (BMDn):

(7) $$RPF_n = \frac{BMD_{IC}}{BMD_n}$$

The RPF is used to calculate the adjusted Exposure (ad-E), which is found for each pesticide by:

(8) $$ad\text{-}E_n = E_n * RPF_n = E_n * \frac{BMD_{IC}}{BMD_n}$$

The cumulative adjusted exposure is then found by summing up the contribution from each pesticide of the CAG:

(9) $$\sum ad\text{-}E_n = \sum E_n * \frac{BMD_{IC}}{BMD_n}$$ which is the same as

(10) $$\sum ad\text{-}E_n = BMD_{IC} * \sum \frac{E_n}{BMD_n}$$

Risk assessment of the cumulative adjusted exposure is made by comparing the calculated exposure (10) to the RV of the Index Compound that is the RVIC.

(11) $$\sum \frac{ad - E_n}{RV_{IC}} = \frac{BMD_{IC} * \sum \frac{E_n}{BMD_n}}{RV_{IC}}$$

By using equation (3) and substituting RV_{IC} for $\frac{BMD_{IC}}{SF_{IC}}$ the risk assessment is expressed as:

(12) $$\sum \frac{ad - E_n}{RV_{IC}} = SF_{IC} * \sum \frac{E_n}{BMD_n}$$

[A similar equation is derived when the NOAELs are used in stead of BMDs.]

That is, if the same safety factors are used for setting the RVs (for common effect) of the individual pesticides (SFIC = SF1 = SF2 = ... = SFn), risk assessments based on the adjusted Hazard Index are exactly the same as risk assessments based on RPFs, assuming that both the RVs and RPFs are based either on BMDs or on NOAELs.

The same safety factor (10*10 = 100) was used in the triazoles exercise and consequently risk assessments based on RPFs should in this example be considered as being at the same tier as risk assessments based on adjusted Hazard Index.