

## **Annex to the minutes of the 94<sup>th</sup> Plenary meeting of the Scientific Panel on Plant Protection Products and their Residues**

### **Recommendations of the PPR Panel on possible future activities supporting the risk assessment of plant protection products**

Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and the Council on Plant Protection Products provides that the approval process of active substances shall be conducted in the light of current scientific and technical knowledge. Therefore the PPR Panel lists in this document a number of activities which should be undertaken to meet this expectation of the legislation.

#### **TOXICOLOGY**

##### **Non dietary cumulative exposure and risk assessment**

From 2007 to 2013 the Panel has elaborated methodologies for the assessment of cumulative risks of pesticides resulting from dietary exposure in the context of Regulation (EC) No 396/2005 on MRLs of pesticides in food and feed.

The regulation (EC) No 1107/2009 provides that cumulative risks resulting from non-dietary exposure need also to be considered. In the recent years EFSA has funded 2 data collections on non-dietary cumulative exposure to pesticides:

- Collection and assessment of data relevant for non-dietary cumulative exposure to pesticides and proposal for conceptual approaches for non-dietary cumulative exposure assessment  
(<http://www.efsa.europa.eu/en/supporting/pub/346e.htm>)
- Collection of pesticide application data in view of performing Environmental Risk Assessments for pesticides  
(<http://www.efsa.europa.eu/en/supporting/pub/en-846>).

After finalisation of the MixTox project of the Scientific Committee (Harmonisation of methods for human and ecological risk assessment of combined exposure to multiple chemicals), the Panel recommends preparing a Scientific Opinion on the science behind the elaboration of a methodology to evaluate the risks resulting from the non-dietary combined exposure to pesticides. This Opinion could include:

- An analysis of the relevance of different modes of combined toxicity (dose addition, response addition, interaction) in the context of non-dietary exposure
- An assessment of the applicability of the methodology for hazard identification and characterisation of specific effects governing the Cumulative Assessment Groups elaborated in the context of dietary exposure
- The elaboration of recommendations for the assessment of non-dietary combined exposure and risk

In addressing these points, the differences between dietary and non-dietary routes of exposure, especially regarding the pattern and level of exposure should be well considered. At longer term, combined exposures from the dietary and non-dietary routes should be aggregated thanks to an appropriate methodology.

### **Developmental Neurotoxicity Testing Strategy**

In its Scientific Opinion on the developmental neurotoxicity potential of acetamiprid and imidacloprid, the Panel made a series of recommendations, including recommendation on the DNT testing framework.

The Panel supports the development of an integrated neurotoxicity testing strategy supplementary to the *in vivo* assay OECD TG 426 in order to screen the DNT potential of pesticides. *In vitro* and non-mammalian alternative systems-based models, along with *in silico* approaches, could provide scientifically robust methods suitable for the initial screening or prioritisation of pesticides for their potential to cause DNT and could also possibly provide a robust point of departure for risk assessment based on read across to known developmental neurotoxic pesticides.

The External Scientific Report (EFSA 2015) on a 'literature review on in vitro and alternative Developmental Neurotoxicity (DNT) testing methods' provides an overview of the scientific state-of-play in this area. In October 2016, a joint EFSA/OECD Workshop on integrated approach for testing and assessment of developmental neurotoxicity took place in Brussels to explore the possibility to establish a battery of in vitro assays for the investigation of developmental neurotoxicity (DNT) potential of chemicals.

The Panel supports the initiated cooperation between EFSA and the OECD on the preparation of guidance on the application and interpretation of in-vitro developmental toxicity assays and definition of a tiered approach to testing and assessment and notes that EFSA contracted an organisation on the implementation and interpretation of in-vitro testing battery for the assessment of developmental neurotoxicity.

As a follow up of these activities, and in line with EFSA 2020 strategy, the Panel is recommending to initiate in 2019 an IATA case study specific for pesticides. The Panel strongly support the initiation of this activity, also considering the level of the experience that EFSA has in this field and the social relevance of the item.

### **Exposure assessment and risk characterisation for Residents**

In 2014, guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products was developed by EFSA. This Guidance identified scenarios for which exposure estimates are least satisfactory, and made recommendations for further research that would reduce current uncertainties, in particular with respect to the exposure of residents.

The Panel concurs to these conclusions and recommends, when a periodical update of this guidance will take place, to consider, with respect to the residential exposure, the following:

- Release and dispersion of pesticide in the air from spraying and from vapour (availability of data or possibilities of modelling/calculation of the amount relevant for resident exposure via inhalation);
- Dislodgeable/transferable residues relevant for residents (foliar/turf/ground deposits);
- Deposition of pesticides onto the ground and Transfer Coefficients related to exposure via contact with contaminated surfaces (leaves/turf/ground);
- Available drift data and refinement possibilities considering the different application methods and crops;
- Meteorological conditions and impact on both the air concentration and ground deposits of pesticides.

Urban amenity areas (UAAs) represent a special situation where intensity of regulation of pesticide use differs across EU countries<sup>1</sup>. These UAAs include roads, roadsides pavements, parks, gardens and sportsgrounds. Although it is thought that the amount of PP products applied to these areas are in general small fractions of the total agricultural use there may be greater exposure of citizens than of agricultural workers in the countryside that wear protective clothing and the exposure may vary according to local or national practices and regulations.

---

<sup>1</sup> KRISTOFFERSEN P, RASK AM, GRUNDY AC, FRANZEN I, KEMPENAAR C, RAISIO J, SCHROEDER H, SPIJKER J, VERSCHWELE A & ZARINA L (2008). A review of pesticide policies and regulations for urban amenity areas in seven European countries. *Weed Research* 48, 201–214.

## **Comparative *in vitro* metabolism studies**

In line with pesticide regulation and data requirements, data on *in vitro* interspecies metabolic differences, including human, are expected to be provided as part of the approval process. These data will be relevant to understand the value of experimental animals in covering human metabolites as part of the risk assessment process. Although methods are available to run the *in vitro* identification of metabolites, specific internationally approved test guidelines are not provided. In addition, due to interspecies differences in expression and spectrum of metabolic enzymes, metabolic clearance and metabolite spectrum of individual pesticides may demonstrate large differences between human and test animals. The Panel recommends the development a guidance indicating the minimum information necessary for developing a study protocol and interpretative analysis for *in vitro* comparative interspecies metabolism. The Panel notes the organisation by EFSA of a technical workshop with key stakeholders in November 2018 which could collect initial information for this purpose.

## **ECOTOXICOLOGY**

### **Birds and Mammals**

In 2009 EFSA published Guidance on the risk assessment for birds and mammals. The Panel is aware of the request of the EC to EFSA to update this Guidance and of the respective agreed Terms of Reference.

Non-dietary routes of exposure are however not covered in the current Guidance. In order to address these routes of exposure, information on dermal and inhalation exposure of birds and mammals was collected through outsourcing an extensive literature review on the topic (<http://www.efsa.europa.eu/en/supporting/pub/637e.htm>). Therefore the Panel recommends taking the following into account in the update of the guidance document:

- The relevance of inhalation and dermal exposure to pesticides for birds and mammals;
- The development of exposure models and recommendations for risk assessment
- The assessment of cumulative exposure and risk for birds and mammals.

Before updating the Guidance it is recommended to clarify with risk managers the specific protection goals for birds and mammals, in particular with regard to long-term (population level) effects. Furthermore it should be investigated whether juvenile life stages are sufficiently protected by the current risk assessment.

The Panel also recommends considering the specific case of bats when the guidance will be updated.

## **Aquatic Organisms**

In 2013 the Panel developed and published Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters.

Later, Scientific Opinions were adopted on the effect assessment for pesticides on sediment organisms in edge-of-field surface water (2015) and on the state of the art of TKTD models for aquatic organisms (June 2018).

Referring to these outputs, the Panel recommends in particular the preparation of Scientific Opinions on:

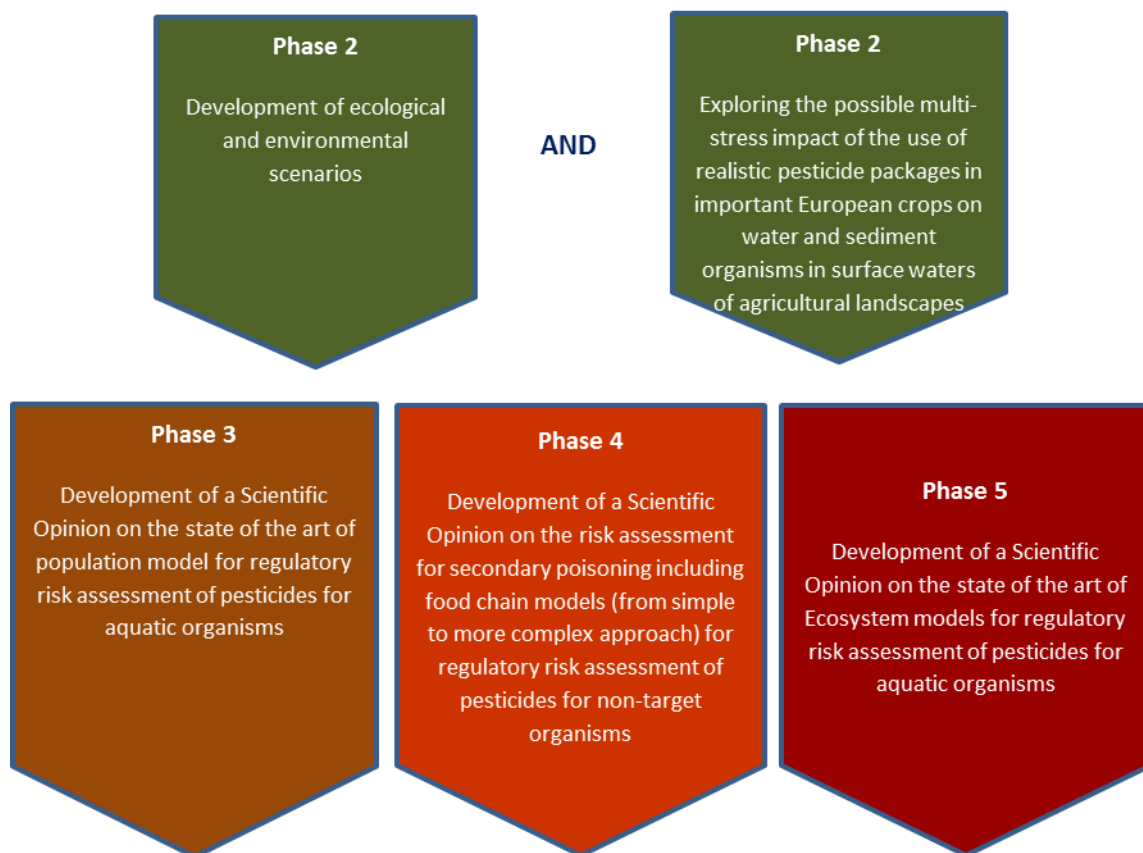
1. Simple food chain models in aquatic ERA;
2. Procedures for the development of ecological and environmental scenarios in aquatic ERA;
3. Use of population models in (landscape-level) aquatic ERA;
4. Decision scheme for the weight-of-evidence approach in aquatic Tier-2 (including the Geometric mean approach);
5. Calibration of the different tiers with (surrogate) reference tier information, with special attention to chronic ERA schemes for pelagic and sediment organisms and the Tier-2C approaches based on refined exposure tests and TKTD models;
6. Update of the decision schemes for metabolites and mixture toxicity;
7. Exploring the possible multi-stress impact of the use of realistic pesticide packages in important European crops on water and sediment organisms in surface waters of agricultural landscapes to explore the feasibility of spatial differentiation in specific protection goals (ETO and ERO option).

In the figure below a road-map is shown including possible activities in the short to long-term plan.

### Short-term plan

- Decision scheme for the weight-of-evidence approach in aquatic Tier-2
- Calibration of the different tiers with (surrogate) reference tier information
- Update of the decision schemes for metabolites and mixture toxicity

### Mid to long-term plan



## Bees

The Panel has assessed the suitability of the BEEHAVE model for its potential use in a regulatory context and for the risk assessment of multiple stressors in honeybees at the landscape level already in 2015. At the time of the assessment, the BEEHAVE model did not include a specific module to simulate effects of pesticide impact. Further developments of the model were published in the last years, exploring pesticide impact on bee colonies.

The Panel has also been informed on the ongoing MUST-B project of the Scientific Committee aiming at developing a holistic approach for the risk assessment of multiple stressors in bees.

The honey bee model in MUST-B is currently the only model designed specifically for environmental risk assessment. In addition, the Panel is aware of further research activities to develop a model for the mason bee (*Osmia bicornis*, former *O. rufa*), which aims at addressing the interactions between this solitary bee and multiple stressors in the environment.

The Panel recommends to integrate the outcome of the ongoing research activities and to explore the coverage of the addressed species also for other pollinators in appropriate follow up actions, in order to make best use of the results in the assessment of the risk of plant protection products for bees.

## Terrestrial organisms (bees, NTA, earthworms, collembolan, etc.)

In its Opinions on the science behind the risk assessment for non-target plants, non-target arthropods and in-soil organisms (EFSA PPR 2014, 2015, 2017), the Panel has proposed risk assessment frameworks that integrate the current state of science and technology to address the risks from pesticide use to these organisms. Especially, uncertainty analyses of standard risk assessment procedures and the approaches to address additional uncertainties at highest assessment steps have been outlined in order to calibrate the proposed tiered approach to the reference tier. It is recommended that uncertainty analyses and calibration of the proposed assessment flowcharts are undertaken, possibly starting with the calibration of the assessment for non-target plants and in-soil organisms. For these organisms, spatial aspects at the landscape level are not of so crucial importance as for e.g. non-target arthropods.

In this respect, it should also be investigated whether latest scientific developments would allow for the proposal and calibration of intermediate Tiers in the risk assessment schemes for non-target organisms (e.g. SSD approaches for in-soil organisms) which have been hampered so far by a lack of available data.



Regarding possible future modelling approaches, the Panel recommends to explore the suitability of TK/TD models for non-target terrestrial organisms. As preparatory work that would also benefit uncertainty assessment in the extrapolation from lab to field, the relationships between exposure, bioavailability, uptake and toxicity of pesticides for terrestrial organisms should be further characterized.

The Panel recommends to further explore the integration of combined toxicity / cumulative risk approaches (e.g. resulting from multiple exposure, products with several actives, tank mixtures, spray schedules) in the risk assessment for terrestrial non-target organisms also at the lowest assessment tiers. Especially in the risk assessment for non-target terrestrial plants no approach to address multiple exposure is currently available at e.g. the screening step.

## **ENVIRONMENTAL FATE AND BEHAVIOUR**

### **Development of realistic worst-case spray drift scenarios for exposure of relevant organisms and for residents and bystanders**

Spray drift scenarios are important for the exposure assessment of non-target aquatic and terrestrial organisms as well as for the human exposure assessment of workers and residents. The spray drift scenarios included in FOCUS surface water are currently being used in almost all exposure assessments. These spray drift scenarios are, however, outdated and do not consider differences in the receiving object (e.g. water bodies or hedges). The Panel in the Scientific Opinions on non-target terrestrial plants and non-target arthropods considered and recommended reviewing new research on spray drift values and to define spray drift scenarios that represent realistic worst-case conditions for exposure of relevant organisms and to workers and bystanders. The literature and data collection on current information on DFR values and spray drift values (Lewis and Tzilivakis, 2017) is the starting point. See <https://www.efsa.europa.eu/en/supporting/pub/1204e>. The Panel considers the following activity relevant:

- Development of a Scientific Opinion on proposals for updated spray drift values and development of methodology to estimate spray drift scenarios that represent realistic worst-case conditions for exposure of relevant organisms and to residents and bystanders.

### **Update of canopy processes including the decline of the dislodgeable foliar residue (DFR)**

For the exposure assessment of non-target terrestrial organisms it is also important to better describe the fate of plant protection products in the plant canopy. An important parameter is the decline of the so called dislodgeable foliar residue (DFR) with time. The Panel recommended in



the Scientific Opinion for predicting environmental concentrations of plant protection products in soil to collect and analyse all relevant literature data on the decline of the DFR in order to further underpin the default value of the DFR half-life. This should be seen in relation to other relevant canopy processes such as crop interception, wash-off and volatilisation. The literature and data collection on current information on DFR values and spray drift values (Lewis and Tzilivakis, 2017) is the starting point. See <https://www.efsa.europa.eu/en/supporting/pub/1204e>.

The Panel finds the following activity relevant:

- Literature/data collection on current information on DFR values;
- Development of a Scientific Opinion on the state of the art of DFR values in relation to development of methodology for measuring and estimating canopy processes relevant for exposure assessment.

### **Development of groundwater scenarios taking new soil maps into account**

The Panel recommended in the Scientific Opinions on the FOCUS groundwater report to re-assess the groundwater scenarios following the scenario selection procedure proposed in the Scientific Opinion on scenario selection and scenario parameterisation for exposure assessment in soil.

The Panel further recommended in the Scientific Opinion on scenario selection and scenario parameterisation for exposure assessment in soil to critically review the organic matter map because it is now well known that the map that is used so far overestimates the organic matter content in arable soils and therefore underestimates leaching to groundwater.

The Panel further identified the need to develop harmonised approaches for landscape-level assessments of leaching to groundwater based on spatially distributed models. Such methodologies could be used to put monitoring data in context or to determine realistic worst-case conditions for individual member states. The methodology should preferably be based on simple models using commonly agreed spatial datasets (conform the dataset developed for the exposure assessment of soil organisms).

The Panel considers the following activities relevant:

- Data collection through e.g. JRC for updating soil, crop and weather data in EU;
- Preparing a Scientific Opinion for a proposal on how the ground water scenarios could be developed taking new soil maps into account.

## **Development of the surface water scenarios taking information on water bodies in EU into account**

The FOCUS Surface Water Scenarios have been developed in the late nineties of the last century and were finalised by 2001 (FOCUS, 2001). Since then, they have proved to be very supportive for the harmonisation of the aquatic exposure assessment in the framework of EU Directive 91/414/EEC and its successor Regulation 1107/2009 at EU level, but there is general agreement that they lack a sound scientific underpinning. Particularly, it is not clear whether the scenarios represent realistic worst-case conditions (e.g. 90th-percentile concentrations within a given area). Moreover, considerable advancement in science and available data has occurred since their development, e.g. the Panel developed realistic worst-case soil exposure scenarios based on GIS-data. The Panel therefore identified an urgent need to develop new surface water scenarios that truly reflect worst-case conditions. In the meantime, a current EFSA Working Group FOCUS Surface Water Scenarios Repair with a limited remit is improving the current scenarios, remediating a number of flaws in these, but this is by no means sufficient to reflect the current state-of-the art in scenario development.

Already in 2005-2007, the Panel recommended in the Scientific Opinions on the appropriateness of using the current FOCUS surface water scenarios (2005) and on the final report of the FOCUS Working Group on landscape and mitigation factors in ecological risk assessment (2007) to make some improvements to the current procedure. The Scientific Opinion on the effect assessment for pesticides on sediment organisms in edge-of-field surface water (2015) also includes recommendations for improvement of the current FOCUS surface water scenarios.

Further the Pesticide Steering Network made a proposal for reconsideration of the surface water scenarios taking into account recent advances in Geographic Information System, EU-wide geographical mapping information (soil data, climate data, data on surface water bodies and land-use data) and of the relevance of the current standard FOCUS water bodies. The Panel finds the following activities relevant:

- Elaboration by the Panel of a proposal for a mandate for a Scientific Opinion developing new surface water scenarios, based upon clear protection goals, further defined in exposure and effect assessment goals. The mandate should include the estimation of a PEC-sediment, the current available spatial and temporal data, a differentiation of water bodies between regions where needed, and the state-of-the art science on scenario development and how to link or integrate ecological scenarios;
- Data collection through e.g. JRC for collecting spatial and temporal data on water bodies in EU;

- Preparing a Scientific Opinion for a proposal on how surface water scenarios could be revised taking spatial and temporal data of water bodies, soil data, weather data and land-use data into account. The proposal should include new spray drift scenarios as described above.

Development of surface water scenarios is relevant for the aquatic exposure assessment to organisms living in water bodies adjacent to fields in the farm land.

## **MICRO-ORGANISMS**

### **Risk assessment for microorganisms, including viruses, used as active substances plant protection products**

This is often problematic and there is very little guidance available. What studies should be requested and how should these be used in the context of risk assessment?

The panel notes that the current data requirements for pesticides using microorganisms including viruses as active substances have not been updated since 2001 (Commission Directive 2001/36/EC of 16 May 2001 amending Council Directive 91/414/EEC) and are considered to be outdated. The current data requirements are not so dissimilar to those of chemical pesticides and do not really fit for microorganisms. Changing data requirements is a long-term goal but recommendations can be made. It was questioned whether the current assessment methodology is fit for purpose. The panel strongly suggests that a Panel opinion is written critically reviewing the appropriateness of current data requirements. It is noted that microorganisms are covered also by other regulations which are assessed by EFSA.

It was suggested that it would be a more meaningful action to address the underlying data requirements rather than providing guidance on the current data requirements. It was noted that additional experts would need to be found for any panel activities in this area. The two 2 External Scientific Reports published by EFSA on literature search and data collection on the risk assessment of microorganisms used as plant protection products for the impact on environment (<http://www.efsa.europa.eu/en/supporting/pub/518e.htm>) and on human health (<http://www.efsa.europa.eu/en/supporting/pub/801e.htm>), respectively, can also be useful background information.

## **OVERARCHING ISSUES**

### **Landscape based environmental scenarios for non-target organisms**

The Panel in its Scientific Opinion on the science behind the risk assessment for non-target arthropods has recommended a risk assessment at the landscape level which considers diverse range of structures and the agricultural practice.

As an initial action to move to a landscape based risk assessment, The Panel 2012-2015 recommends preparing Scientific Opinions on the development of EU landscape-based environmental/ecological scenarios.

These Opinions could make use of the information generated by the External Scientific Report (<http://www.efsa.europa.eu/en/supporting/pub/en-846>) on a collection of pesticide application data in view of performing Environmental Risk Assessments for pesticides.

As a first step it is proposed to define the procedures on how to derive the environmental scenarios. It is recommended that quantified specific protection goals are elaborated before developing such environmental scenarios. The landscape based environmental scenarios to be developed should be usable in Guidance documents and compatible with modelling activities.

In this activity, the environmental specificities of the rice cultivation should be considered and covered in order to address concerns and recommendations of the Scientific Committee on Plants in its Opinion adopted on the 30th January 2003. Proposals of the Pesticide Steering Network for the revision of the Med-Rice Guidance ([https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides\\_ppp\\_app-proc\\_guide\\_crop\\_rice.pdf](https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_crop_rice.pdf)) should for this purpose be taken into consideration.

### **Optimising controlled experiments in regulatory risk assessment of pesticides**

A controlled experiment is an experiment in which the variable factors are controlled so as to make it possible to observe the result of varying one factor at a time. Positive control experiments establish that a negative outcome of an experiment is not a result of a poor process, while negative control experiments establish that a positive outcome is not the result of a poor process.

Regulatory studies essentially include negative control experiments. The interpretation of their results often considers both the observations in the concurrent control experiment and historical control data, which do not

meet the absolute criteria of a proper control as they are not contemporaneous with the comparison experiment and so not identical in all respects except the change under study. A consistent and appropriate approach is needed in this process.

Therefore, the Panel recommends the preparation of a Scientific Opinion investigating the use of negative control experiments and their role in regulatory testing. This Scientific Opinion is intended to investigate, discuss and give recommendations on experimental design and laboratory testing, minimal requirements for control experiments and use of historical control data focusing on studies relevant to pesticides authorization. In addition, the review of present practice is expected to reveal opportunities to optimise the risk assessment to achieve greater scientific excellence.

### **Endocrine disruptors – development of AOPs**

The EFSA/ECHA guidance for the identification of endocrine disruptors in the context of Regulation (EU) No 528/2012 and (EC) No 1107/2009 is expected to implement the scientific criteria for the determination of endocrine-disrupting properties of biocidal products and plant protection products in June and November 2018 respectively. A key element of the guidance is the identification of ED effects and the link with an endocrine mode of action. The Panel recognize that the pragmatic approach described in the guidance will benefit of the availability of endocrine mediated adverse outcome pathways (AOP). The use of the AOP conceptual framework will allow for a scientific validation of endocrine pathways linking molecular initiating events (MIEs) to the observed adverse effects. The AOP conceptual framework is chemically agnostic and this would allow flexibility when dealing with chemically specific MOA analysis. As the observed adverse effects could be consequent to multiple MIEs leading to common intermediate key events (KEs), developing AOPs for endocrine mediated pathway will help in postulating the MOAs, identify data gaps and the most appropriate investigation i.e. mechanistic strategy. Therefore, the Panel strongly recommends developing AOPs for both EATS as well as for non-EATS mediated endocrine effects.

### **Uncertainties in the risk assessments of plant protection products**

In its 86th meeting, the Panel discussed a pilot study on the inclusion of uncertainty analysis in the reasoned opinions on the modification of pesticide maximum residue levels and supported the implementation of uncertainty analysis in the area of pesticides.

The Panel recommends the preparation of reference documents identifying and assessing the generic uncertainties inherent to the standard procedures and models used in the various types of risk

assessments (for humans and the environment) conducted in the context of Regulation 1107/2009. The Uniform Principles provide indeed that the interpretation of the results of evaluations takes into consideration possible elements of uncertainty in the information obtained during the evaluation, in order to ensure that the chances of failing to detect adverse effects or of under-estimating their importance are reduced to a minimum.

This work should be conducted with respect to the precise assessment questions and respective desired level of protection, so that an appropriate calibration of the assessment methods is enabled.