Grant Agreement No: 245163
Project start date: July 2010
Project end date: November 2013

ACROPOLIS

Aggregate and Cumulative Risk Of Pesticides: an On-Line Integrated Strategy

SEVENTH FRAMEWORK PROGRAMME

Deliverable 6.9 A report summarizing the connection between ACROPOLIS, EFSA and DG Sanco including the Scientific Lecture and discussions with DG Sanco

The dissemination level changed from Public to Confidential because informal letters or minutes are included in the deliverables, The letters or minutes prove that we have delivered what has been promised but were not announced as being openly available at the time we discussed these issues.

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1. EFSA reply to RIVM on ACROPOLIS project initiatives

European Food Safety Authority

SCIENTIFIC EVALUATION OF REGULATED PRODUCTS DIRECTORATE

Parma, 9 September 2013
Ref: PB/LM/CB/ms (2013) out - 7857754

Mr Jacob D van Klaveren National Institute for Public Health and the Environment (RIVM)
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Subject: Response to the letter received from RIVM on the 12th of July 2013

Dear Mr. van Klaveren,

Thank you for your letter on the current status of the Acropolis project and the initiatives relevant to the activities within the framework of hazard and exposure modelling taken by RIVM.

Further development and harmonisation of risk assessment methodologies is an important task of EFSA and involves scientific cooperation with Member States and international bodies in the field of food and feed safety.

EFSA is currently in the process of developing methodologies for cumulative risk assessment. So far, the work has focused on the methodologies for conducting cumulative hazard assessment and is still ongoing. The outcome of the hazard assessment will highly determine the requirements for performing cumulative exposure assessment. At present, the software tools and models that can perform such an assessment need-to-be- explored:· Specifically;- the tools need-to be manageable f-er-in-house data aeress-units-and in line with previous EFSA scientific opinions and guidance documents as well as it must fit into the regulatory decision making process regarding MRL setting.

EFSA is in the starting process of exploring the area of cumulative exposure assessment and appreciates the initiatives taken within the ACROPOLOIS Project as this project might feed well into the work by EFSA on cumulative exposure assessment. EFSA looks forward to the outcome of this exercise and anticipates having an open-dialog with RIVM on any updates about future EFSA activities within this area.

Yours sincerely,

Per Bergman
Director

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2. ACROPOLIS midterm review and User Group Initiative

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Date 26 September 2012
Subject ACROPOLIS Midterm Review and User Group Initiative

Dear Hubert,

With this letter I would like to update EFSA on the progress made within the ACROPOLIS project and to inform you on our User Group Initiative. I can inform you that the European Commission (DG Research) has recently finalized the midterm review of the ACROPOLIS project with a positive and encouraging outcome. The ACROPOLIS project was considered well-organised, ambitious and the involvement of all relevant stakeholders was judged as a very positive signal to justify the European funding.

Furthermore, the European Commission was very pleased to see that so many Member States, not originally being partners of the ACROPOLIS project, have asked to become associated with the ACROPOLIS project on their own initiative. The involvement of Member States, including their willingness to share data owned by them, will be further formalised in official Agreements. These Agreements are necessary to facilitate the needs of the different stakeholders.

We have a procedure in place to handle all data of the Member States. Once they have indicated their willingness to share data with ACROPOLIS the Member States write a letter to EFSA's DCM unit granting access to their data. We are very pleased with the help from EFSA's DCM unit and Pesticide Unit in providing consumption and/or monitoring data to us once access has been granted by the data-owners. It is an efficient way of working together and the harmonised approach might facilitate future exchange or even transfer of the software developed within ACROPOLIS to EFSA. EFSA may consider the ACROPOLIS results useful for implementing the full cumulative pesticide risk assessment as a routine requirement in the regulatory process.

DG Research made two major recommendations in their midterm review:

1. to start to work with user groups in an early stage in order to gain maximum profit of this EU project;
2. to fine-tune as much a possible with DG Sanco and EFSA and discuss how they will benefit from the results of the EU project.

DG Research has asked the ACROPOLIS consortium to draft a plan on how user roups might start using the ACROPOLIS software from November 2012 onwards. We have submitted the user group initiative plan to DG Research describing the main goals and objectives for each user group initiative and DG Research have accepted this plan recently. The first outlines of the user group initiative were shared with the ACROPOLIS External Advisory Board (Luc Mohimont and Bas Drukker).

Recently Luc Mohimont has updated me on the status of the EFSA opinion on Guidance on how to use Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues. Luc also made us aware of the discussions between EFSA and DG Sanco about practical issues. Following the DG Research recommendation, we hope to help both EFSA and DG Sanco as much as possible in the last year of the ACROPOLIS project for example by familiarizing stakeholders on how to use the ACROPOLIS software to follow the EFSA guidance in practical terms. In the very short term we will post an E-learning tool (or practical hand book to use the software) on the ACROPOLIS website. This E- learning tool is a contractual deliverable to DG Research. Secondly we will start working with user groups according to the User Group Initiative.

Part of the User Group Initiative is that pesticide industry needs to have access rights to monitoring data to be used as input for the risk assessment in combination with relevant data of their new pesticides under research. Once they are confident that they can pass the criteria set in the EFSA guidance they might decide to share their data and risk assessment results with European regulators and EFSA. Regulators have to check the correctness of the risk assessment again according to the EFSA guidance. The ACROPOLIS platform has separate sections, one for confidential data and one section on which data can be shared. The European Crop Protection Association (ECPA) and nearly all major companies in Europa and USA are involved and will attend a meeting planned in the Netherland.

The developments regarding the EFSA guidance and the need of stakeholders like pesticide industry have been included in the User Group Initiative. The selection of the case study might result in useful experience to all stakeholders involved and hopefully this can optimise the cumulative risk assessment methodology in practical terms.

The User Group Initiative consists of the following items:

1. We will start working with three user groups on a confidential basis from November onwards.
2. The first user group consists of the pesticide industry companies. This group has to calculate the risk according to EU Directives and then has to submit their risk assessment results to the regulatory process. They will be given access to the ACROPOLIS models and consumption or monitoring data owned by the Member States[1].
3. The second user group consists of the European regulators. We plan to discuss the needs of this user group with Fransesca Arena and Michael Flueh in October this year. Regulators will be familiarized with the

[1] Please note that MCRA software is paid by the Dutch Ministries with large contribution of the European Commission. We won't ask fees for future use of the software to avoid any conflict of interest. We are not a commercial software company.

usefulness and meaning of the results of the probabilistic assessment in comparison with the current deterministic assessment. This experience will also focus on the impact for decision making.

4. The third user group consists of the national food authorities. They will be familiarized to use the EFSA guidance for the calculations of actual risk using monitoring data.
5. All user groups will be working with triazole data as a kind of second case study following the first case study being part of the EFSA opinion. The new case study will address all multi-compound modelling and the input needed for cumulative exposure assessments as a kind of follow up of the first case study. We selected triazoles as a case study to be closely in line with the EFSA 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.
6. Training for EFSA staff (Pesticide Unit and DCM) to be planned in November. Initially this was planned for April/May 2012 but Luc Mohimont has suggested performing the training with a more final version of the ACROPOLIS models.

I hope to have you informed sufficiently about the midterm review and the User Group Initiative. I would very much welcome your comments and your view on how we can plan the last period of ACROPOLIS in such a way that it is profitable to EFSA.

Sincerely yours,

Jacob van Klaveren
Coordinator ACROPOLIS

3. EFSA letter Hubert Deluyker

European Food Safety Authority

SCIENCE STRATEGY AND COORDINATION DIRECTORATE

Parma, 22 OTT, 2012
Ref HD/LM/jr (2012) – out – 6892136

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Re: ACROPOLIS Midterm Review and User Group Initiative

Dear Jacob,

Thank you for your letter of 26 September informing us about the progress and the success of the ACROPOLIS project. This project is of very high interest to EFSA with regard to the future implementation of cumulative risk assessment for pesticides as required by Regulation (EC) 396/2005.

As you know, the PPR Panel has adopted a guidance on the use of probabilistic methodology for modelling dietary exposure to pesticide residues, which was just published a few days ago. Therefore now is the perfect time to consider how to make optimal use of the last part of the ACROPOLIS project to support the regulatory risk assessment of pesticides, as recommended by DG Research in the midterm review of the project.

Important questions on the borders of Risk Assessment, Risk Management and Risk Communication are still open before regulatory cumulative risk assessments can be done. The definition of the relevant regulatory questions, of the desired levels of consumer protection and the respective appropriate parameterisation of the models are the most important ones.

Considering the wide adhesion of Members States to the ACROPOLIS projects, the already initiated exchange of data between EFSA and the ACROPOLIS consortium, and the clear support of the Commission to the delivery of an integrated web-based risk assessment tool accessible for all stakeholders under work package 5, I suggest and would welcome an intensive cooperation between the ACROPOLIS consortium,

DG SANCO and EFSA in the final steps of the project. The External Advisory Board, including representatives of DG SANCO and EFSA, seems to be the most appropriate forum for this.

Your intention to provide training to EFSA staff as part of the User Group Initiative is also much appreciated.

Yours sincerely,

Hubert Deluyker
Director

cc Catherine Geslain-Laneelle, P.Bergman, H.Fontier, L.Mohimont

4. EFSA Scientific colloquim on Cumulative and Aggregated Pesticide Risk Modelling

Cumulative and Aggregated Pesticide Risk Modelling, the ACROPOLIS-project
EFSA Scientific Colloquium 18-10-2012
Jacob van Klaveren, RIVM. The Netherlands.

Current risk assessment of pesticides and MRL setting does not sufficiently account for cumulative and aggregate exposure (Regulation (EC) 396/2005). The central **aim** of the ACROPOLIS project is to improve risk assessment strategies in Europe. The project will develop a framework for cumulative and aggregate risk assessment of pesticides that is scientifically sound and accessible for all actors involved in European risk assessment and risk management.
This work consists of: 1) studying the data needs, data availability and organization including uncertainties for cumulative exposure and effect assessment in a **probabilistic risk assessment** framework; 2) integrating models describing various routes of exposure into an **aggregate exposure** model; 3) setting up **new toxicological** testing for identifying possible **additive or synergistic** effects and developing a **strategy** for refinement of cumulative assessment groups; 4) integrating **cumulative and aggregate risk models** including uncertainty analyses in a web-based tool, including accessible data for all stakeholders; 5) **improving risk assessment strategies** in Europe by analysing stakeholders attitudes, by training and by discussing the new methodology in several stakeholder conferences.

The first stakeholder conference was perceived as very successful by all stakeholders. It included fruitful contributions from DG Sanco, EFSA, EPA, WHO, Food Authorities, NGO's and Pesticide Industry and a member of the European Parliament very positively encouraged the project. Follow-up actions have been taken since in close cooperation with the stakeholders responsible for pesticide risk assessment, as well as with DG Research.

The stakeholder involvement and the ACROPOLIS risk assessment approach will be explained during the Scientific Lecture. Many member states, as partner or having approached the ACROPOLIS project to become associated with it, will start testing the models and cooperation with EFSA is discussed.

All models are so called 'higher tier' approaches and require intensive statistical cooperation. A few ACROPOLIS models, including the model for cumulative exposure assessment, will be ready for implementation by the end of the project, whereas others like internal dose modelling and aggregated exposure assessment will need further research.

Other examples of 'higher tier exposure modelling' in relation to EFSA tasks will be shortly highlighted.

5. Report Second ACROPOLIS stakeholder conference

Second Stakeholder Conference

Brussels, 15 October 2013

Current MRL settings do not take into account cumulative and aggregate exposure. In 2010 the ACROPOLIS project was set up under the support of the Seventh Framework Research Programme to address aggregate and cumulative risk of pesticides and to build an on-line integrated strategy in Europe.
After three and a half years of intense cooperation between the various partners, the project is delivering its outcome. Following a first ACROPOLIS stakeholder conference in February 2012, which aimed to discuss the conceptual modeling approach and implementation of the new models, a second stakeholders conference was organized in Brussels on 15th October 2013. The aim of this second stakeholder meeting was to discuss the ACROPOLIS achievements and its future relevance for stakeholders.

The **central aim** of the ACROPOLIS project is to develop new cumulative and aggregated exposure models and to set up a new toxicological way of testing to confirm assumptions made in the current risk assessment related to mixtures of the pesticides. The developed models in the ACROPOLIS project are programmed in a coherent way and will become available via a web-based platform. The ACROPOLIS platform includes data needed for the cumulative and aggregated risk assessment in Europe. This is referred to as the ACROPOLIS IT tool. The IT tool is scientifically sound, transparent and validated. The tool will become accessible for all actors involved in the European risk assessment and risk management after finalization of the project at the end of November 2013.

The ACROPOLIS stakeholder conference attracted close to 70 delegates from both the public and private sector. Under the leadership of RIVM member of the board of directors, Annemiek van Bolhuis, a programme for the second ACROPOLIS stakeholder conference was structured to inform attendees on the achievements of the ACROPOLIS project, and to discuss the way forward regarding:

1. the European context and the achievements of ACROPOLIS;
2. addressing cumulative risk assessment and the experience of different user groups;
3. future perspective on aggregate exposure and toxicological testing;
4. general reflection including the perspective of the fresh produce sector and how the ACROPOLIS models might fit into the future perspective of RISK21;
5. conclusions and way forward.

This report is a brief synthesis of the proceedings of a full day discussion.

A summary of the ACROPOLIS project are available on the ACROPOLIS website

http://acropolis-eu.com/about-the-project/summary/ and recommendations can be found under the link http://acropolis-eu.com/about-the-project/recommendations/

The slides of the presentations given during the ACROPOLIS stakeholder meeting are also available on-line on the ACROPOLIS project website: http://acropolis-eu.com/news-events-training/events/2nd-stakeholder-meeting/

Session 1: The European context and the achievements of Acropolis

The first session featured several speakers including **Annemiek van Bolhius**, member of the board of directors of RIVM. She highlighted that the important issue of risk assessment of co-exposure to pesticides is a pending duty, which needs to be fixed in the near future. During the first ACROPOLIS stakeholder meeting, the European Parliament member Carl Schlyter inspired the project and asked to fix the hole in the European legislation as soon as possible. Today lectures will be presented as a follow-up to the first stakeholder conference.

The ACROPOLIS project aims to provide an adequate tool for risk assessment and risk management so that future consumers might gain confidence in the regulatory process and the legislation on pesticide safety evaluations. Annemiek van Bolhuis thanked the European Commission and EFSA for their support throughout the last three and half years of the project. She also thanked the various project partners for their dedication and professional expertise brought to the ACROPOLIS project.

The European Commission representative, **DG SANCO director Eric Poudelet**, stressed the relevance of the ACROPOLIS project for the safety assessment of the food chain and for the support that the project brought to the European Commission's commitment to protect European consumers against hazards. According to Eric Poudelet, ACROPOLIS has not only produced a new innovative model for pesticide risk evaluation, but also brought excellent cooperation throughout Europe. The cooperation between the member states and stakeholders involved in the safety evaluations is appreciated. Fostering cooperation in a European project, increasing transparency in risk assessment and data sharing among stakeholders involved, is the way forward. Furthermore, the ACROPOLIS project connects innovation in the area of complex model development to practical needs and expectations of the European Commission. Therefore, DG SANCO sees a project such as ACROPOLIS as best practice at the European level.

The European Commission has a strict policy on pesticide authorization taking into account sustainable use, as well as the need for harmonization of pesticide evaluations. The European policy has led to a reduction of the use of pesticides. However, the issue of multiple residues of pesticides has not been considered yet in risk assessment and risk management due to the lack of the methodology so far. The Commission is well aware that this is an important issue and considers the ACROPOLIS project a major step forward in order to enable the Commission to take action and to respond to societal concerns. While the requirement is already enshrined in legislation, information technology and sophisticated models are not available to stakeholders, yet. The director of DG SANCO is pleased to see the ACROPOLIS project has delivered such an IT tool today and that cumulative risks assessment can be performed at the international level as a follow-up of the ACROPOLIS project. Eric Poudelet made a plea for a quick implementation of the ACROPOLIS model into the daily practices of institutes and stakeholders responsible for pesticide risk assessment. The good cooperation established during the ACROPOLIS project's evolution should be continued.

Djien Liem (EFSA) elaborated on the perspective of the European Food Safety Authority (EFSA) on the dossier of cumulative risk assessment. EFSA is involved in risk assessment of mixtures of pesticides since 2006 and EFSA published a scientific opinion on the suitability of existing methodologies to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs in 2008. In

2009, a scientific opinion was released on cumulative risk assessment of the triazole group as atest of the proposed methodologies and to gain experiences with it. In 2012, EFSA released the guidance on the use of probabilistic methodology for modeling dietary exposure to pesticide residues. This guidance is not an official EU guideline but provides guidance to users of probabilistic models help to gain practical experiences based on good science. Finally, in 2013 EFSA opened a public consultation on the Scientific Opinion on the identification of pesticides to be included in cumulative assessment groups based on their toxicological profile. EFSA will adopt a final opinion on the relevance of dissimilar mode of action related to cumulative risk assessment and its appropriate application. Currently, EFSA is testing the methodology of probabilistic exposure assessment with new or already existing software to identify the most suitable future approach for EFSA needs.

EFSA will evaluate on a regular basis the implementation of risk assessment guidance documents already developed within EFSA. If needed, actions will be taken by EFSA to develop new guidance for approaches where adequate guidance is considered necessary, to update and enhance the implementation of the guidance where needed. This process is referred to as the guidance life-cycle. In this context, the EFSA Scientific Committee recently released an opinion on priorities for guidance development. High priority guidance documents for 2014-2015 are the use of weight of evidence approach for risk assessment, the biological relevance (adaptive *vs* adverse response) and harmonisation of the assessment of human exposure. This opinion will be shared with national and international risk assessment bodies within and outside Europe to avoid duplication of efforts and to identify opportunities to strengthen harmonisation of risk assessments at international level.

Djien Liem provided an overview of the activities of the Data Collection and Monitoring (DCM) Unit of EFSA promoting data collection in the form of Standard Sampling Descriptions. The DCM unit tests out several exposure assessment methodologies including improved data collection based on a Total Diet Study approach. The DCM unit is EFSA key-unit to collect data and to perform exposure assessments together with the various units of EFSA which are dealing with chemical risk assessments.

Djien Liem thanked the ACROPOLIS project for its useful achievements and cooperation.

An overview of the ACROPOLIS project achievements was given by the ACROPOLIS coordinator **Jacob van Klaveren (RIVM).** He reminded the particular background under which the project was developed and he highlighted the main objective of the project, namely to improve cumulative and aggregated risk assessment in Europe. The project has developed new risk cumulative and aggregated risk assessment models accessible via a web-based tool. This IT tool includes accessible data for all stakeholders responsible in the process of pesticide risk assessment in Europe.

Jacob van Klaveren stressed the significant involvement in the project of stakeholders, National Health and Safety Institute and Food Safety Authorities at the member state level, which was not foreseen in the initial project plan. Many member states felt the need to be connected to the ACROPOLIS project as an associated partner and decided to contribute with data to the project achievements on their own costs. For the reason of international cooperation and stakeholder involvement, the European Commission requested to reframe the ACROPOLIS project and to offer training to potential end-users such as pesticide industry, NGOs, national food authorities and regulatory bodies.

The cumulative and aggregated exposure models are compatible with the European infrastructures of data collection. The final ACROPOLIS cumulative exposure model is now nearly ready for release and the model is in line with the EFSA guidance on the use of probabilistic modeling for dietary exposure to pesticide residues. The beta version of the ACROPOLIS cumulative exposure models is already in use in an increasing number of European countries including ongoing discussion on improving practicalities. Next to the ACROPOLIS cumulative exposure assessment via food, the ACROPOLIS project has also delivered a PB-PK model in order to predict the internal dose of exposure after being exposed to two different pesticides simultaneously or to extrapolate from in vitro concentrations to in vivo doses. The PB-PK model is also accessible via the Internet, however, PB-PK model development should be seen as a proof of principle. Today the connection between external and internal dose modeling is in principle possible, but this is in a very early stage of development and needs further investment to be explored.

A number of ACROPOLIS model validation studies are still ongoing but these studies are in a finalizing stage. One of the validation studies compares the ACROPOLIS model with the DEEM model currently in use by the Environmental Protection Agency (EPA) in the United States of America. The validation exercise demonstrates an interest in the ACROPOLIS model also outside the European Union. The ACROPOLIS model offers opportunities of increased transparency in risk assessment and management practices. Several user group representatives have already said that the cumulative model should be considered as a useful instrument to discuss the level of protection needed in Europe. Jacob van Klaveren thanked the ACROPOLIS partners for their enthusiastic and useful contribution of the last three years

After the three lectures, a short debate was organized. The audience addressed questions about the future perspective and relevance of the ACROPOLIS achievements. Eric Poudelet stated that the ACROPOLIS project helps to better adhere to society expectation allowing for better evaluating the risk of pesticides in the European Union. The project's achievements will provide confidence within and outside the European Union. The European Union is the world leader in both import and export of agricultural and agrifood produce and therefore continuation of the ACROPOLIS achievements is important to the European Commission.
Djien Liem said that he is impressed by the progress made in the ACROPOLIS project and that the project has contributed to current and future needs in line with EFSA guidance and strategy.
Jacob van Klaveren highlighted the worldwide interest in the ACROPOLIS model and he mentioned already ongoing collaboration with Brazil, interest from WHO, China and Australia as well as ongoing discussions about improvements in the cumulative exposure methodology with the Environmental Protection Agency (EPA) of the USA.

Session 2: Addressing cumulative risk assessment and the experience of different user groups

This session reviewed the new ACROPOLIS IT tool addressing cumulative exposure assessment via food. The two main users of the software for setting Maximum Residue Limits (MRL) and to establish safe use of new pesticides are pesticide industry and the regulators, including EFSA peer reviewing draft reports of the member states. National Food Authorities and NGOs have been trained or have been offered training in an early stage of the ACROPOLIS project and further training tools will become available to

them after the project ends. The speakers in this session evaluated the experiences and lessons learnt by the different user groups and their view on the way forward.

Introducing the session, **Polly Boon (RIVM)** provided an overview of the ACROPOLIS IT tool and its achievements on cumulative exposure modeling. The presentation addressed the key elements of the Monte Carlo Risk Assessment (MCRA) IT tool. This tool follows the EFSA guidance on probabilistic modeling including an optimistic and pessimistic model run. The presentation also addressed the goal of WP2 of ACROPOLIS to generate an e-platform of input data for the stakeholders involved in pesticide risk assessment in Europe, and to use the developed tool to estimate the cumulative exposure to a group of triazole pesticides according to the requirements of the EFSA guidance.

The IT tool was tested and proved to be user-friendly and easy to operate, and able to assess acute and chronic cumulative exposure. The optimistic model was easy to apply, while the performance of the pessimistic model run was more laborious because a lot of additional data is required to fulfill all the details in the EFSA guidance. During the project this has been a struggle to follow the pessimistic requirements, but based on the experience a workable approach was achieved. Certain assumptions made in the EFSA guidance turned out to result in unrealistic results, like the assumption of including MRLs for animal products resulting in a more than 50% contribution of these commodities to the overall exposure.

Based on the experience it was recommended to consider an intermediate “realistic” scenario combining the optimistic and pessimistic model run. It was also recommended to gain more experience with the EFSA guidance and the ACROPOLIS IT tool with larger Cumulative Assessment Groups.

Monika Bross (ECPA/BASF) reported about the experience of the industry user group . Her presentation was made on behalf of seven leading EU and USA pesticide manufacturers. The user group of pesticide industry started to get experience with the ACROPOLIS IT tool from December 2012 onwards. Since then the seven companies have organized meeting on two occasions and had bi-monthly teleconference for exchanging and agreeing on testing procedure using the ACROPOLIS IT tool. Furthermore, the industry user group closely cooperated with the ECPA Expert group on toxicology and the two working groups worked on common view of developing a higher tier dietary exposure assessment procedure for cumulative risk assessment.

The main focus of the user group tests was on acute exposure for single compound (triazole fungicide) using European consumption data and the user group became familiar with the probabilistic tool MCRA software 8 (also referred to as IT tool of ACROPOLIS). They were able to enter their own company specific compound information and compared results generated with deterministic and probabilistic approaches. During the evaluation, the calculation procedures of MCRA and DEEM were directly compared by using US consumption data. The industry user group was very pleased to see how the ACROPOLIS IT tool can be used with the data from two different continents, because it helps to harmonize procedures in pesticide risk assessment. The industry user group studied the impact that the different input parameters such as processing and variability factors had on the results of probabilistic modeling.
Although the pesticide industry companies were able to upload their data to the ACROPOLIS IT tool, a more automated procedure is recommended.

Monika Bross shared the view of pesticide industry companies on the way forward with the audience. Today there is a large volume amount of consumption and monitoring data available in the ACROPOLIS IT tool, but still data from key-countries such as Germany can make the tool even more valuable in the near future. A plea was held to regularly upload all EU monitoring data collected in EU/national programs in order to maintain the usefulness of the IT tool in the nearby future. While the ACROPOLIS IT tool is easy to use, probabilistic assessment itself is, however, still a very complex process. A more straightforward and general accepted 'cook book' complementary to the current EFSA guidance is highly recommended. This 'cook book' should explain calculations steps in easy-understandable language to non-experts. The help offered by the experts of the ACROPOLIS project was always very timely and appreciated by the industry companies. The EFSA on-going work establishing new common assessment groups needs to be reflected in the future ACROPOLIS IT tool.

In conclusion, industry companies felt that probabilistic modeling is necessary for cumulative risk assessment and that the ACROPLIS project has brought the relevant IT tools and data accessible to industry. Monika Bross recommends discussing the pending issues between DG Sanco and all relevant stakeholders, before deciding to implement probabilistic modeling in a regulatory framework. That discussion should also address intentions to work towards one agreed procedure over Europe and inclusion of realistic assumption related to the input variables. Furthermore, the European Commission should strive for a set of basic criteria for risk managers to decide on the required level of protection. The USA experience herewith, might be helpful to guide Europe through the still open discussion in how to implement probabilistic modeling in future risk management practice in Europe.

Paul Hamey (HSE-UK) reported on the experience collected by the regulators user group. The regulators were trained in May 2013 following an invitation of the European Commission. Paul Hamey started with a reviewed of the history, the current state of the art and future direction in probabilistic risk assessment and risk management needs from the perspective of European regulators.

Prior to the ACROPOLIS project experiences were already gained both in the UK and in the USA on probabilistic modeling. Probabilistic assessments were explored in several European funded projects such as the Monte Carlo project, SAFE Foods and the current ACROPOLIS project. In the early part of the century the EU regulatory framework changed significantly with the launch of EFSA , acceptance of MRL regulation 396/2005, and new PPP regulation 1107/2009 including articles describing the future regulatory obligation to address cumulative and aggregated exposure assessment. EFSA organized a colloquium on cumulative assessments, which was followed by publications of several EFSA opinions (criteria for cumulative assessment, triazole study, guidance on exposure assessments needed for cumulative dietary assessments, identification of CAG). EFSA is in the lead to set and to finalize the cumulative risk assessment methodology.

The ACROPOLIS project is well received by the regulatory process because it addresses complexities of factoring multiple sources of exposure from a wide range of related compounds. Despite all the complex issues, the ACROPOLIS IT tool is now user-friendly and it is possible to follow the EFSA guidance on the use of probabilistic modeling for dietary intake to pesticide residues using the ACROPOLIS IT tool. It enables implementation of cumulative dietary assessment, following the approaches recommended by EFSA into the risk management deliberations in Brussels. Furthermore, ACROPOLIS also provides an approach to consider non-dietary pathways in addition to the cumulative exposure assessment.

Representatives of nearly all EU member states were trained and the general feeling is that ACROPOLIS is a useful tool for the assessment of cumulative exposures to multiple compounds via food in the coming year(s). However, still a number of issues related to the acceptance and final use in risk assessment needs to be considered by the regulators and the Standing Committee on the Food Chain and Animal Health of DG SANCO. These issues are, among other things, related to uncertainty in the data and input variable and the required level of protection to be set in the European Union.

For aggregated exposure, the methodology is still in its infancy. It is therefore recommended to gain more experience and to include robust pesticide usage data and behavior patterns of operator, worker, bystander and resident into the aggregated exposure models. In a follow-up of the ACROPOLIS project, the stakeholders and DG SANCO should secure the achievements of the project for better risk assessment and risk management of real risks in Europe, while avoiding additional complexity, precaution and cost with little benefit. In addition we should strive for acceptance of probabilistic modeling within the European Commission decision making process.

To complete this user group review, **Jorgen Schlundt (Director DTU Denmark**) presented the perspectives of the food authorities on the ACROPOLIS achievements. This presentation first reminded the organization of risk assessment, risk management and risk communication including national and international food safety institutes and responsibilities. Specificities of chemical and microbiological risk assessment were highlighted. Where the microbiological risk assessment had a more refined modeling approach compared to chemical risk assessment ten years ago, the ACROPOLIS project now shows that chemical risk assessment has potentially improved.

Jurgen Schlundt emphasized that human risk assessment of combined exposure to multiple chemicals poses several challenges including the complexity of the terminology and problem formulation. Furthermore, the diversity of chemical entities and the toxicological profiles and exposure pattern share complicated issues to be included into today's risk assessment. The probabilistic modeling approach set by ACROPOLIS can be seen as a good example not only for pesticides but also for all types of chemical risk assessment. Particular focus was drawn on the need and relevance of an international perspective on this issue of cumulative exposure assessment. Therefore, we should look at other national experience outside Europe and we also should see the project in perspective of WTO standards (SPS agreement) or CODEX developments. Today, a big step forwards is set with the ACROPOLIS IT tool presented, but the tool and issues should also remain open for continuous improvement. The current tool is certainly not the final stage of developments.

Jurgen Schlundt made a plea not to forget the importance of risk communication. Often risk managers and scientist believe that probabilistic exposure assessment is too complicated for consumers, but this might be a misunderstanding. Consumers will be able to understand results of probabilistic modeling, but it is necessary to include consumers and their perception of risk into the risk management discussions and decisions.

The session was finalized with a lively debate. The audience and the speakers discussed issues about how to improve the use of the ACROPOLIS model for risk management practice and how to improve some practicalities in current use of the ACROPOLIS IT tool. Suggestions were given on extrapolating the ACROPOLIS model experience to other international organizations including FAO/WHO and how to get

other international organization connected to a harmonized approach (e.g. via collaborating WHO centers and/or US EPA involvement).

Session 3: Future perspective on aggregate exposure and toxicological testing

The cumulative exposure model produced by ACROPOLIS is now a workable concept in line with EFSA guidance. Aggregated exposure assessment, as defined in the ACROPOLIS project, refers to exposure assessment via different routes e.g. skin, inhalation and food. Aggregated exposure assessment is still in its infancy and todays discussions are mainly related to improving non-dietary exposure. However, the legislation also requires aggregated exposure assessment to be implemented in future risk assessment and risk management. In this session two speakers looked at the future perspective on aggregate exposure in risk assessment and how ACROPOLIS can contribute to that future needs. The third speaker elaborated on new toxicological testing in relation to confirm the assumption of dose-addition made in current EFSA methodology and also to narrow the number of pesticides in a common assessment group.

Richard Glass (FERA-UK) presented the achievements of the ACROPOLIS project with respect to aggregated exposure model for pesticide risk assessment. Aggregate exposure is an estimate of the exposure of a defined population to a given compound by all relevant routes and from all relevant sources. This includes exposure via the diet, via the skin (dermal) and via inhalation. Different scenarios can be defined for occupational exposure of operators and workers, incidental exposure of bystanders and residents (often living adjacent to farm land), and use of amateur or consumer products in the home and garden.

Several collaborative projects have contributed to the improvement of data collection and concepts for aggregated exposure assessment. Results of these projects are becoming available now. In addition to the ACROPOLIS project, Richard Glass highlighted the FP7 Browse project on improving models for non-dietary exposure to pesticide of bystanders, residents, operators and worker. For aggregated exposure assessment, several aspects need to be considered amongst which are mentioned the toxicological properties of the pesticides e.g. acute or chronic toxicology, and use patterns of pesticides in agriculture.

Richard Glass presented several case studies. The first case study illustrates a combination of dietary exposure and occupational exposure for UK operators to the triazole group of compounds. The ACROPOLIS IT tool combines the non-dietary and dietary exposure input together and the output of this case study was presented in understandable output graphics and diagrams. A second case study illustrates the combination of exposure of a pesticide used in agriculture and which pesticide was also present in consumer products. In this case study the output for non-dietary exposure is generated using the ConsEXPO model and the outputs was linked to the dietary exposure for a defined population group. The aggregate ACROPOLIS model allows for flexibility in the input and the output selections.

Although the first experience with the aggregated exposure models seems promising, a number of critical data gaps were identified for both exposure data and use patterns. Most critical data gaps were identified and the need for these to be addressed in the future. An EFSA funded project aiming to collect

farm survey data for cumulative risk assessment for plant protection product CFT/EFSA/PPR/2010/04) was highlighted as a good example to make this possible.

Sebastian Denys and Valerie Pernelet (ANSES –France) presented an example of how exposure via food and exposure via environmental contamination can be combined in an aggregated exposure assessment. They showed a case study using the chemical bisphenol A, which occurs as a contaminant in food and the environment. The presentation outlined the current single chemical and single source approach as being the state of the art in today's risk assessment approaches. However, bisphenol A is present in different concentrations in several food items, in air dust and air. Exposure assessment via different routes requires additional information regarding absorption factor after inhalation and bioavailability factors after oral ingestion. Finally, results of the exposure assessments needs to be summed and expressed on an internal dose dimension in the human body. PB-PK models are necessary to elaborate on potential metabolism and distribution of bisphenol A within the human body before the chemical poses effect on the critical target organ.

ANSES worked on a conceptual overview of all potential sources and routes relevant for exposure to bisphenol A. In a second step, ANSES identified relevant input data either coming from existing database such as exposure data from the French Total Diet Study or from literature research. The final bisphenol A hazard characterization was based on a peer review of all available data including a bioavailability factor for bisphenol A after oral ingestion and a skin absorption factor.

The case study addressed the exposure of bisphenol A to pregnant women. The bioavailability of bisphenol A was assumed as high as 3% after oral ingestion for food and an adsorption factor of 100% for exposure via inhalation. The results are expressed as a probabilistic distribution showing a major contribution to the total internal exposure dose from food (84%), air (12%) and dust (4%).

ANSES concluded that aggregated exposure is a challenge for all of us and not only for pesticide risk assessment. The aggregated exposure assessment can be improved in the future by including more uncertainty analyses or links with bio-monitoring data and/or PB-PK modeling. Furthermore, a link with other population groups and a standardized approach to link aggregated models with exposure data in France or various member states in a standardized manner is highly recommended.

Angelo Moretto (University of Milan) completed the section with a lecture addressing the new toxicological in-vitro testing performed in the ACROPOLIS project. The aim of the work is to define which pesticides should be included in the common assessment group of triazoles and group of pesticides affecting neurotransmission. A second aim was to test the dose-addition assumption for mixtures of pesticide exposure. Furthermore, the work on toxicology testing in ACROPOLIS elaborated on the usefulness of PB-PK models for estimating internal exposure: this was applied to both extrapolation from in vitro concentrations to in vivo doses ("reverse dosimetry"), and to estimate exposure once a consumer is exposed to two pesticides simultaneously.

Angelo Moretto highlighted the results of the in-vitro study. A nice dose-response relationship was seen for the tested pesticides triadimefon and flusilazole. Apart from the pesticides tested, a mixture of both pesticides was added to the test system. A stronger effect was observed compared to the separate effect of the single chemicals, but the magnitude of the effect of the mixture was according to expectation based on the dose-additivity assumption made in the EFSA guidance.

In vitro test are also very helpful to narrow down the number of pesticides assumed to belong to a common assessment group. Furthermore, in vitro testing helps to reduce the number of animal testing. However, in-vitro test results are not always quantitatively the same as in vivo results. Compounds are activated or metabolized via different pathways or with different efficiency. Therefore, in-vitro to in vivo extrapolation is not always straightforward and in-vitro validation with in-vivo experiments are necessary to validate in-vitro experiments. Within the ACROPOLIS project, the University of Milan has performed such a validation study. Angelo Moretto highlighted a few results and he recommends gaining more experience with finding the correct scaling factor between animal in-vitro testing and the real human situation.

Within the ACROPOLIS project, a PB-PK model was developed addressing exposure to two pesticides simultaneously. The PB-PK model also allows for entering information of exposure via different routes. The PB-PK model is internet compatible and in future developments the PB-PK model and the exposure modelling presented by Polly Boon might be linked directly. The PB-PK model was very helpful to link in vitro data with the in vivo situation and for the interpretation of the toxicological findings resulting from a field study, which was set up for validation reasons. In this field study relevant exposure routes were measured such as exposure via skin and via a duplicate diet study as well as the concentration of the pesticide in urine. The measured and predicted aggregated exposure results are not ready now, but will be published in a scientific paper after the project has ended.

Session 4: General reflection including the perspective of the fresh produce sector and future developments in science

In this session, two presenters reflected on the usefulness of ACROPOLIS in future developments or future needs for trade and science. The first presentations focused on the problems in the European market related to pesticide residue regulation. The second presentations focused on the usefulness of ACROPOLIS models in the perspective of developments in new toxicological testing and interpretation of results in the RISK21 project.

Axel Moehrke (Dole Fresh Fruit /Freshfel Europe) presented the views of the fresh fruit and vegetables sector on the need of trust in legislations and the role of cumulative exposure assessment to cover for multiple pesticides. The consumption of fresh produce witnessed an on-going decline over the last decade. This trend is the result of several factors, including the consumers concerns about pesticide residues, driven by scaremongering approach inspired by NGO campaign. In contrast, the fresh produce industry has never been today as conscious about its food safety responsibility adopted Good Agricultural Practice (GAP) practices certified by quality scheme. Besides, and following the harmonization of Maximum Residue Limits (MRL), the compliance with the MRL has reached a very high level in recent years.

However, the development of lab technics, the emergence of new grey areas in the legislation such as the confusion between the Acute Reference Dose and Maximum Residue Limits and the omission of cumulative risk assessment, has resulted in the use of different pesticides to cope with the different

pest/fungus in agriculture. This development has introduced new uncertainties in trade and motivated a number of retailers to introduce private standards

According to the trade organizations, the ACROPOLIS project is an important new milestone to provide greater confidence in the EU regulatory process and give additional confidence for consumers in the legislative process. Axel Moehrke reminded the audience that the IT tool developed by ACROPOLIS should be for the benefit of public stakeholders in the MRL decision and recognized tool to improve food safety risk decisions.

To conclude the presentation of this second stakeholder conference, **Alan Boobis (Imperial College -UK)** presented his views on the ACOPOLLIS model in future perspective in RISK 21. RISK 21 is a new discussion aiming to transform toxicological testing and risk assessment towards more mechanism based approaches. It also aims to reduce the amount of animal testing and to start the process of risk assessment based on the relevance of outcomes of exposure observations. The RISK 21 discussion started in the USA based on three reports of the National Research Council and leading scientists reviewing the developments and future needs in toxicology and risk assessment in the 21th century.

Alan Boobis highlighted the progress made in a number of areas, including QSAR and omics technology, to screen chemicals for their toxicological properties. In addition to screening tools, 'in vitro' testing increases the possibility of confirming toxicological profiles. New cell culture approaches were also highlighted in the lecture. Observed effects in vitro, however, cannot always be translated to toxicological effects in the human body in a straightforward manner. To complement the observations in 'in vitro' testing systems, PB-PK modeling, scaling factors to transform toxicodynamic information from animals to humans and a more mechanistic based pathway approach are therefore needed.

The key principles of RISK 21, as far as they relate to the ACROPOLIS achievement presented today, are among other things a well-defined problem formulation, a tiered approach to exposure estimates and a tiered approach to toxicity hazard assessment. The results of the exposure and hazard assessment are plotted in a two dimensional plot in such a way that they are understandable for non-experts. The matrix is graduated from an area of minimal concern (green = low exposure, low toxicity) to one of high concern (red - high exposure, high toxicity) Chemicals falling to the intermediate zone are of potential concern, and the need for further refinement will be context dependent, as provided in the problem formulation. For a given chemical, the matrix plot gives an immediate indication of whether refinement of the exposure estimates or of the toxicity estimates will have the greater impact on the assessment. The risk from mixtures can also be visualized in this two-dimensional plot, including the influence of uncertainty on the estimates.

According to Alan Boobis, the ACROPOLIS project has already made major contributions to the objectives of RISK 21. First of all several of the 'in vitro' tests and the PB-PK models provide good proof of principle of how the toxicity of mixtures can be tackled in a efficient manner. The RISK 21 tiered approach to exposure assessment ranges from simple screening methods in tier 0 to biomonitoring in tier 3. In the RISK 21 scheme, probabilistic exposure assessment is considered a tier 2 approach and the

ACROPOLIS IT tool showed today that higher tier exposure assessment is becoming available in Europe in a form that is accessible to stakeholders.

Conclusions and the way forward

After a full day of presentation and animated discussion following each session, several conclusive remarks were made and suggestions for the way forward were done. These are reported below on a non-exhaustive basis and without being classified in a ranking of relevance:

- ACROPOLIS is an important IT tool to support the regulatory process and enhance confidence in its outcome. DG SANCO and EFSA are keen to have such a cumulative risk assessment methodology incorporated in Europe.
- EFSA and DG SANCO will discuss how the final methodology and the current IT tool might be useful in the final methodology to be set by European institutes.
- A number of suggestions were made to harmonize the cumulative exposure assessment worldwide. It is important to continue progressing gradually and step by step. First, the ACROPOLIS IT tool needs to be accepted by regulators in the Member States who need to gain more experience with the IT tool in risk management practice.
- DG SANCO proposes to set up an electronic WG with Member States' experts to address both short term and long term issues on cumulative risk management, as it needs experience of regulators before incorporating this concept in MRL setting.
- ACROPOLIS can help to discuss risk management decisions about the required level of protection. This helps to make legislation more open and understandable for European citizens.
- The cooperation between the ACROPOLIS project and Member States not original involved in the project is appreciated and should preferably continue.
- Aggregate exposure modeling is part of the innovation, but remains in its infancy. Within the coming four years, EFSA and/or Member States might benefit from the first prototype already developed as part of the ACROPOLIS project.
- DG SANCO suggested that ACROPOLIS partners should act as ambassadors of the IT tool in their national environment. There is a need to increase the awareness of the work that has already been done based on European funding. . Practical application and exercises should not only be done at EU level, but also at national level to gain experience with the new methodology in the Member States.
- The EFSA PPR panel should look at the current state of play on cumulative risk assessment, not only from a scientific perspective but also to be workable and practical.
- The Member States should help to improve on future data availability.
- DG SANCO highly recommended RIVM and EFSA to cooperate on further implementation of the ACROPOLIS IT tool in Europe.

The chairwoman for the day, Annemiek van Bolhuis closed the meeting with thanks to the delegates for attending, to the speakers for sharing their expertise with the participants. She also thanked Freshfel Europe for the good organization of the meeting.