COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Paper for Information:

Aggregate and cumulative risk of pesticides: an on-line integrated strategy (ACROPOLIS)

Introduction

1. The FSA provided matching funds to co-fund the Food and Environment Research Agency (FERA) as one of the partners involved with the ACROPOLIS project. It was anticipated that the ACROPOLIS project would build on the output of a previous FSA-funded project that considered cumulative and aggregate exposure to mixtures of pesticides and veterinary medicines from all potential exposure pathways[1]. In particular, ACROPOLIS addressed some of the recommendations previously made by the COT for research to support risk assessment of mixtures of pesticides and similar substances[2].

2. An information paper about the EU project ACROPOLIS (TOX/2011/14, attached at Annex A) was provided to the COT at its March 2011 meeting. The objectives and partners of this three-year project, which started in June 2010, with the aim to develop a framework for cumulative and aggregate risk assessment of pesticides that is scientifically sound and accessible for all those involved in the risk assessment and risk management in Europe is outlined in Annex A.

ACROPOLIS Update

3. The ACROPOLIS project was completed in November 2013. In 2012, FSA staff attended training in probabilistic modelling which embraced aspects of the ACROPOLIS project. FERA subsequently presented some of the project results at the Agency's risk assessment workshop in March 2015. The presentation showed that the project had developed new methods and software to estimate risks from cumulative exposure, i.e. from multiple

[1] T10005: Estimation of human uptake of pesticides and veterinary medicines from all potential exposure pathways http://tna.europarchive.org/20130814101929/http://www.food.gov.uk/science/research/foodcomponentsresearch/mixturesresearch/t10prog/T10projlist/t10005/

[2] The outcome of a Working Group for the Risk Assessment of Mixtures of Pesticides/Veterinary Medicines established by the COT in 2001. http://cot.food.gov.uk/committee/committee-on-toxicity/cotwg/wigramp

chemicals in the diet, and aggregate exposure from non-dietary sources. The presentations demonstrated how MCRA (Monte Carlo Risk Assessment) software had been adapted, so that dermal, oral or inhalation exposure could be combined with dietary exposure within the ACROPOLIS model. The aggregate model had been tested based on a biomarker and duplicate diet study carried out in Italy (grapevine sprayers). Examples were also used to illustrate the aggregate model using UK and Dutch input data.

4. In May 2015, eight articles on ACROPOLIS were published in *Food and Chemical Toxicology - Special issue on Toxicity testing and model development for estimating cumulative and aggregate exposure to pesticide residues in Europe.* The titles of the articles and highlights are listed below:

i. The ACROPOLIS project: Its aims, achievements, and way forward.
This article concludes that the project delivered an IT tool that was perceived as user-friendly by potential users.

ii. The MCRA model for probabilistic single-compound and cumulative risk assessment of pesticides.
This paper describes models and a MCRA software system available for stakeholders in pesticide risk assessment developed in the ACROPOLIS project. It shows that additional data on agricultural use of pesticides may give more realistic risk assessments.

iii. Cumulative dietary exposure to a selected group of pesticides of the triazole group in different European countries according to the EFSA guidance on probabilistic modelling. Highlights from this paper include:

- Modelled the cumulative dietary exposure to triazoles in eight European countries.
- Tested the practicality of the EFSA guidance on probabilistic modelling for cumulative exposure assessments.
- Optimistic model run can be performed on a routine basis for cumulative assessments.
- Pessimistic model run is very laborious and may result in very conservative exposure estimates.
- More experience is needed with the EFSA guidance regarding feasibility of all requirements and need for conservatism.

iv. A European model and case studies for aggregate exposure assessment of pesticides. Highlights from this paper include:

- A flexible framework is presented to calculate aggregate pesticide exposure.
- Dietary and non-dietary sources can be included from multiple routes and chemicals.
- The model is implemented within web-based software.
- Seven case studies are presented from three EU countries and existing models/data.

- The examples include a combination of operator, bystander and consumer activities.

v. Testing a cumulative and aggregate exposure model using biomonitoring studies and dietary records for Italian vineyard spray operators. Highlights from this paper include:
   - Tests of a new multi-source and multi-compound exposure model are presented.
   - Comparisons cover dermal, dietary and urine samples from a biomonitoring study.
   - Intermediate model calculations are compared with a range of existing models.
   - Modelled cumulative dietary exposures are consistent with duplicate diet measurements.
   - Modelled aggregate exposures are broadly consistent with field measurements.

vi. New approaches to uncertainty analysis for use in aggregate and cumulative risk assessment of pesticides. Highlights from this paper include:
   - Uncertainty in aggregate and cumulative pesticide exposure are considered.
   - A general strategy is presented to prioritise and handle uncertainties.
   - Examples including dietary and non-dietary exposures are illustrated using MCRA.
   - A new method is described to combine pesticide usage and monitoring data.
   - Alternative approaches to quantify uncertainty and variability in 2-Dimensional Monte Carlo Simulation are discussed.

vii. The use of *in vitro* testing to refine cumulative assessment groups of pesticides: The example of teratogenic conazoles. Highlights from this paper include:
   - A dose-additivity assumption at doses around the NOAEL proved correct with teratogenic conazoles.
   - *In vitro* studies can be used to refine cumulative assessment groups of chemicals.
   - Effects of combined exposures can be extensively tested *in vitro*.

viii. Stakeholder attitudes towards cumulative and aggregate exposure assessment of pesticides. Highlights from this paper include:
   - Current monitoring of pesticide residues is perceived to be adequate.
   - Timeliness and consistency of monitoring of pesticide residues are questioned.
   - Need of using pesticides and problematic nature of exposure to residues are acknowledged.

- Understanding of cumulative exposure assessment (EA) is better than aggregate EA.
- ACROPOLIS' perceived relevance and expected outcomes are evaluated favourably.

5. Information on where to obtain copies of the journal articles is attached at Annex B.

Euromix project: follow-up to ACROPOLIS

6. The Euromix (European Test and Risk Assessment Strategies for Mixtures) project, which started in May 2015, will extend MCRA and the models developed in ACROPOLIS,. Food and pesticides will again be one of the main priorities, but the project will scale up the implementation so that it can be used in more realistic scenarios. Non-dietary aggregation will also be considered, by linking MCRA with some existing non-dietary exposure models. The Chemicals Regulation Directorate (CRD) of the Health & Safety Executive is also involved in Euromix. FERA and CRD's tasks have not been precisely defined yet. A press release on the project kick-off is attached at Annex C.

7. The Agency will continue to keep a watching brief on further work in this area.

Further Information

8. Further information on ACROPOLIS is available on its website - http://www.acropolis-eu.com/.

Secretariat
June 2015

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A copy of the above paper, TOX/2011/14 is attached below:


tox201114.pdf

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Aggregate and cumulative risk of pesticides: an on-line integrated strategy (ACROPOLIS) - http://www.acropolis-eu.com/

Further information

Papers from ACROPOLIS special issue of Food and Chemical Toxicology Volume 79, May 2015:

i. Jacob D. van Klaveren, Marc C. Kennedy, Angelo Moretto, Wim Verbeke, Hilko van der Voet, Polly E. Boon. The ACROPOLIS project: Its aims, achievements, and way forward. Food and Chemical Toxicology, May 2015 (79): 1-4.
The journal article above is available to purchase from the link below:
http://www.sciencedirect.com/science/article/pii/S027869151500085X

ii. Hilko van der Voet, Waldo J. de Boer, Johannes W. Kruisselbrink, Paul W. Goedhart, Gerie W.A.M. van der Heijden, Marc C. Kennedy, Polly E. Boon, Jacob D. van Klaveren. The MCRA model for probabilistic single-compound and cumulative risk assessment of pesticides. Food and Chemical Toxicology, May 2015 (79): 5-12.
The journal article above is available to purchase from the link below:
http://www.sciencedirect.com/science/article/pii/S0278691514004360

iii. Polly E. Boon, Gerda van Donkersgoed, Despo Christodoulou, Amélie Crépet, Laura D'Addezio, Virginie Desvignes, Bengt-Göran Ericsson, Francesco Galimberti, Eleni Ioannou-Kakouri, Bodil Hamborg Jensen, Irena Rehurkova, Josselin Rety, Jiri Ruprich, Salomon Sand, Claire Stephenson, Anita Strömberg, Aida Turrini, Hilko van der Voet, Popi Ziegler, Paul Hamey, Jacob D. van Klaveren, et al. Cumulative dietary exposure to a selected group of pesticides of the triazole group in different European countries according to the EFSA guidance on probabilistic modelling. Food and Chemical Toxicology, May 2015 (79): 13-31
The journal article above is available to purchase from the link below:
http://www.sciencedirect.com/science/article/pii/S0278691514003767

iv. Marc C. Kennedy, C. Richard Glass, Bas Bokkers, Andy D.M. Hart, Paul Y. Hamey, Johannes W. Kruisselbrink, Waldo J. de Boer, Hilko van der Voet, David G. Garthwaite, Jacob D. van Klaveren. A European model and case studies for aggregate exposure assessment of pesticides. Food and Chemical Toxicology, May 2015 (79): 32-44
The journal article above is available to purchase from the link below:

http://www.sciencedirect.com/science/article/pii/S0278691514004104

v. Marc C. Kennedy, C. Richard Glass, Silvia Fustinoni, Angelo Moretto, Stefan Mandic-Rajcevic, Patrizia Riso, Aida Turrini, Hilko van der Voet, Michel T. Hetmanski, Richard J. Fussell, Jacob D. van Klaveren. Testing a cumulative and aggregate exposure model using biomonitoring studies and dietary records for Italian vineyard spray operators. Food and Chemical Toxicology, May 2015 (79): 45-53.
The journal article above is available to purchase from the link below:

http://www.sciencedirect.com/science/article/pii/S0278691514005213

vi. Marc C. Kennedy, Hilko van der Voet, Victoria J. Roelofs, Willem Roelofs, C. Richard Glass, Waldo J. de Boer, Johannes W. Kruisselbrink, Andy D.M. Hart. New approaches to uncertainty analysis for use in aggregate and cumulative risk assessment of pesticides. Food and Chemical Toxicology, May 2015 (79): 54-64.
The journal article above is available to purchase from the link below:

http://www.sciencedirect.com/science/article/pii/S0278691515000472

vii. Angelo Moretto, Francesca Di Renzo, Erminio Giavini, Francesca Metruccio, Elena Menegola. The use of in vitro testing to refine cumulative assessment groups of pesticides: The example of teratogenic conazoles. Food and Chemical Toxicology, May 2015 (79): 65-69.
The journal article above is available to purchase from the link below:
http://www.sciencedirect.com/science/article/pii/S0278691514003305

viii. Wim Verbeke, Ellen J. Van Loo, Filiep Vanhonacker, Ilse Delcour, Pieter Spanoghe, Jacob D. van Klaveren. Stakeholder attitudes towards cumulative and aggregate exposure assessment of pesticides. Food and Chemical Toxicology, May 2015 (79): 70-79.
The journal article above is available to purchase from the link below:
http://www.sciencedirect.com/science/article/pii/S0278691514004335

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Press release: EuroMix project kick-off

EUROMIX
newsmessage.pdf

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