European Food Safety Authority

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Pesticide risk assessment at the European Food Safety Authority
New developments

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Evaluation of the toxicological relevance of pesticide metabolites and degradates in the absence of animal testing data

Structure of the presentation

- Regulatory framework
- Introductive consideration
- PPR Panel activities and research funded by EFSA

Regulatory framework

EU Regulation (Dir. 91/414/EEC & Reg. (EC) 1107/2009) concerning the placing on the market of plant protection products sets out uniform principles for the evaluation and decision-making regarding plant protection products.

- The likely risk to human, animals and the environment need to be addressed.
- Assessment of the risk for the consumer is a major part of this process.
- This requires the identification of the *relevant* metabolites and degradates of the active substances present in food commodities and an assessment of the associated risk.

Sources of metabolites and degradates.

- Plant metabolism
- Animal metabolism
- Microbial activity in soil
- Abiotic processes, including processing of food commodities

Investigation through a range of regulatory studies

Pesticide use results in the dietary exposure to a wide range of different chemicals.

Toxicological data

- Active substances: full toxicological dossier, allowing establishment of toxicological reference values

- Metabolites and degradates: very limited in the majority of cases

- **Need consider a priori that not only the toxicological potency but also the nature of toxicological effects may differ**
- **Need to minimise the use of animals in toxicological testing**
- **Potential difficulties in synthesising technical material**
- **Cost**
- **Overall limitation in research capacities**

OECD guidance document on the Definition of Residue (Series on Pesticides, No. 31; Series on Testing and Assessment, No. 63)

For each pesticide, 2 residue definitions

- Residue definition for monitoring, indicator compound concept
- Residue definition for risk assessment, reflecting the actual toxicological burden

- **Gives general principles for the identification of metabolites relevant for risk assessment combining toxicological and exposure considerations**
- **Implementation difficult, inconsistencies when comparing evaluations of different advisory bodies.**
- **Which tools available for this?**

PPR Panel mandate

EFSA asked the PPR Panel in October 2008 to address the toxicological relevance of metabolites and degradates of active substances of plant protection products

- Including a review and evaluation of alternative toxicological tools
- With a view to develop in a later step a guidance document based on an appropriate combination of the relevant tools.

PPR Panel program of work

- 1. Outsourcing of exploratory activities – 2009/2010
  - Applicability of the Thresholds of Toxicological Concern concepts.
  - Applicability of computational methods (Q)SAR Analysis and expert systems
  - Impact of metabolic processes on the toxicological properties of active substances

- 2. Opinion – 2010/2011: Scientific opinion on approaches to evaluating the toxicological relevance of metabolites and degradates of pesticide active substances in dietary risk assessment

- 3. Guidance document on the establishment of the residue definition for risk assessment in food commodities – 2011/2012

Outcome of the TTC project (Chemicals Regulation Directorate, UK).

- Survey amongst regulatory and advisory bodies: TTC is not widely used but there is no *a priori* reason why it could not be used.

- Selection of the scheme of Kroes (2004) as a sound basis for pesticide metabolite assessment.

- **1st Step (0.15 µg/person/day)* : Compounds with genotoxicity alerts or data.**
- **2th Step (18 µg/person/day): OP structure**
- **3th Step (90 µg/person/day): Substances meeting the criteria for Cramer Class III classification.**
- **4th Step (540 µg/person/day): Substances meeting the criteria for Cramer Class II classification.**
- **5th Step (1800 µg/person/day): Substances meeting the criteria for Cramer Class I classification.**

*** After exclusion of the COC compounds**

Outcome of the TTC project (Chemicals Regulation Directorate, UK).

- Validation of the scheme of Kroes against the ADI of 100 pesticide active substances, wide range of endpoints and chemical classes. Slight changes appropriate for pesticide.

- **1st Step (0.15 µg/person/day)* : Compounds with genotoxicity alert or data.**
- **2th Step (18 µg/person/day): Extension of OP structure to a broader neurotoxicity category.**
- **3th Step (90 µg/person/day): Substances meeting the criteria for Cramer Class III classification.**
- **4th Step (540 µg/person/day): Substances meeting the criteria for Cramer Class II classification.**
- **5th Step (1800 µg/person/day): Substances meeting the criteria for Cramer Class I classification.**

*** After exclusion of the COC compounds**

- Adequate protection following adjustment of the neurotoxicity threshold.

Outcome of the TTC project (Chemicals Regulation Directorate, UK).

- Case studies performed for 15 pesticides

- **The TTC scheme was able to derive from the 79 metabolites identified a reduced set of 16 compounds that required further consideration (63 metabolites were below their respective TTC)**

Outcome of the TTC project (Chemicals Regulation Directorate, UK).

- Issues:

- **(Q)SAR predictions did not correlate well with the toxicology profile of pesticide active substances**
- **Uncertainties in exposure predictions**
- **How to deal with acute exposure in the TTC concept?**

Outcome of the QSAR project (Institute for Health and Consumer Protection, JRC).

- Survey on how QSAR analysis is used by national regulatory bodies and international advisory organisations

- **38 respondents including government authorities and industry**
- **Majority of respondents do not currently apply QSAR analysis on a routine basis.**
- **Lack of in-house expertise**
- **In case of use, mainly for priority setting and filling data gaps in urgent situations**
- **Respondents generally support wider use and request further guidance and training**

Outcome of the QSAR project (Institute for Health and Consumer Protection, JRC).

- Extensive review of QSAR potentially useful in dietary risk assessment, focussing on toxicological end points and ADME properties.

- **Availability of models variable (many for genotoxicity and carcinogenicity – very few for organ toxicity).**
- **Each model described for their descriptors, applicability domain, availability, implementation in software tools, associated documentation regarding the model development and validation process.**

Outcome of the QSAR project (Institute for Health and Consumer Protection, JRC).

- Development of a framework for assessing the usefulness of QSAR models as support to dietary risk assessment in regulatory context summarized in a checklist of questions:

- **Clarity of the endpoint to be predicted**
- **Relevance of the endpoint to the regulatory purpose**
- **Availability of the training set for statistically based models**
- **Documentation on the method supporting the model development**
- **Performance of the model**
- **Reliability of predictions for analogues**
- **Information on the applicability domain (physicochemical, structural and mechanistic data)**

Outcome of the QSAR project (Institute for Health and Consumer Protection, JRC).

- Research investigations on the potential use of (Q)SARs as filter to efficiently identify genotoxic and carcinogenic compounds in the TTC scheme

- **Several data sets were used: pesticides, DSSTox Carcinogenic Potency Database, dataset of classified mutagen according to the EU classification process.**
- **Interesting results were obtained with combination of models to identify classified mutagens with good sensitivity and possible optimisation of the predictions.**

Outcome of the QSAR project (Institute for Health and Consumer Protection, JRC).

- General recommendations:

- **Need to investigate applicability (predictivity & scope) of different software tools on an endpoint by endpoint basis**
- **Need to explore the advantages of combining multiple tools**
- **Need of policy decisions on how much information is needed to use the models in regulatory decisions**
- **Need of criteria regarding model acceptability (e.g., minimum sensitivity….)**
- **Need of guidance on how to interpret the outputs of models**
- **Need of training.**

Outcome of the project on the impact of metabolic processes on the toxicological properties of active substances (AGES – Austrian Agency for Health and Food Safety).

- Exhaustive review of metabolic transformations for 11 classes of pesticides including 56 active substances.

- **About 140 specific chemical changes identified but no trend observed in terms of 'toxification' or 'detoxification'**
- **Low amount of data for individual changes**
- **Lack of toxicological data for metabolites**

- No robust information found in public literature.

Outcome of the project on the impact of metabolic processes on the toxicological properties of active substances (AGES – Austrian Agency for Health and Food Safety).

- Development of criteria to evaluate when and how toxicological data on active substances cover mammalian metabolites.

- **Possible criteria:**
  - **the measured amounts of metabolites**
  - **notion of metabolic pathways**
  - **assessment of systemic exposure**.

- **Possible areas of improvement in the planning and/or use of ADME studies to provide useful information.**

Conclusion:

Useful information has been gathered and is currently evaluated by the PPR Panel