Analytical methods for monitoring of biocides in the environment – are the data requirements sufficient?

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Outline

- Introduction

- Evaluation of Residue Analytical Methods
  - Choice of matrices
  - Choice of analytes (residue definition)
  - Required validation data

- Confirmatory methods

- Multi-residue methods

- Summary and conclusion
Why are biocides detected in milk?

Introduction

Example: Residues of DDAC in food

- Request to BfR for analytical methods for DDAC in food material

Information from EU Assessment (draft CAR):

“The DDAC containing product ... is not intended for use in areas where food for human consumption is prepared, consumed or stored, or where the feedingstuff for livestock is prepared, consumed or stored...”

Are the data requirements sufficient?
General data requirements biocides


- Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 (shall apply from 01/09/2013)

Detailed explanation of individual endpoints

- Technical Guidance Document (October 2000)

Introduction

Analytical methods *in all relevant environmental media* including recovery rates and the limits of determination for the active substance, and *for residues thereof*, and *where relevant* in/on the following [Ann. IIA, IV.4.2.]:

(a) Soil
(b) Air
(c) Water
(d) Animal and human body fluids and tissues

Which compounds belong to “residues thereof”?
Which environmental media are relevant?
Evaluation of analytical methods for monitoring

Which matrix is relevant?
- residue definition -

Which analytes are relevant?

Which action values (LOQ) must be achieved?

Contamination of water, soil or sediment possible?
Relevant metabolites known?
Environmental fate and behavior
NOEC of most sensitive species (surface water)
No proposal for sediment
Place and type of application of the product
Composition of the active substance
Stability of a.s., DT90 <3 d?
EU drinking water limit (0.1 µg/L)
Soil: general limit 0.05 mg/kg

a.s. = active substance
Which matrices are considered relevant?

- Active substances approved for PT8 (wood preservatives):
  
  Acceptable residue analytical methods available for:
  
  - Soil: 28 substances
  - Air: 20 substances
  - Drinking water: 25 substances
  - Surface water: 24 substances
  - Sediment: 5 substances out of 31 a.s. accepted for Annex I

- No common set of required methods.
- Waiver for non-submission, e.g. a.s. in ionic form (cyanide, boron salts) not in all cases available.
- In some cases data gaps should be filled at product authorization.
- No clear rules for additional matrices, e.g. marine sediment, sea water …

Discussion and harmonization necessary!
Definition of relevant analytes (residue definition)

Product type 18: Insecticides, acaricides and products to control other arthropods

Inclusion in Annex I/IA decided: 17 active substances

Not considered: carbon dioxide, nitrogen, bacillus thur., hydrogen cyanide

In 30 % of relevant cases the residue definition (RD) was not discussed.
Why is a discussion of the residue definition necessary?

- 1st Example: **Margosa Extract**

  Azadirachtin A is the main component of extracts isolated from seeds of the Neem tree (*Azadirachta indica)*

- Further components: Azadirachtin B, Aazadirachtin H, Nimbin, Salanin, Desacetyl-Nimbin, Desacetyl-Salanin, Fatty acids

- Composition of Neem extract strongly depends on the manufacturing process.
Why is a discussion of the residue definition necessary?

- 2nd Example: Creosote

„Creosote is a complex mixture of hundreds of distinct compounds, …The chemical composition is influenced by the origin of coal and also by the nature of the distillation process… . 106 compounds have been analysed for in the creosotes applied for.”

Source: Assessment Report, chapter 2.1.1, December 2010

Definition of one or more marker substances is necessary!
Why is a discussion of the residue definition necessary?

- 3rd example: N,N-Dimethyl sulfamide (DMS)

Other cases:
- Active substance is not stable in the environment (DT90 < 3d).
- Residues of toxic or ecotoxic by-products occur.

Residue definition should include relevant metabolites, conversion products and degradation products.
Data requirements for analytical methods for monitoring

... are listed in:

- **TECHNICAL GUIDANCE DOCUMENT (October 2000)**


- Additional guidance on:
  TNsG on Data Requirements, Part A, Chapter 2, Point 4 “Analytical Methods for Detection and Identification” and Part B, Chapter 2, Point 4 “Methods of Identification and Analysis” (May 2009)

Which validation data are necessary?

Selectivity: Matrix interferences, blank value, confirmation

Recovery: 2 fortified concentration level, 5 samples per level

Precision: relative standard deviation of the recoveries per level

Calibration: Calibration line, raw data, equation of function

LOQ: Defined as lowest fortified level with acceptable recovery

Chromatograms: Blank samples, fortified samples at LOQ, standard chromatograms

…and a clear documented description of the method and the validation!

General extent of validation comparable to the procedure for authorization of plant protection products (SANCO/825/00 rev. 8.1), but differences…
Frequent dissent: the type and extent of confirmation

- **Requirement for Biocides**

  “… demonstration of selectivity, unless highly specific techniques are employed …”

  - What is a “highly specific technique”?
  - What is meant by “demonstration”?
  - Which data are necessary to demonstrate “selectivity”?

  ![Graph](image)
Frequent dissent: the type and extent of confirmation

- **More explicit requirement for Pesticides:**
  “…confirmation, that the right analyte is detected *and* the signal is quantitatively correct …”

- Includes qualitative and quantitative confirmation.
- Validation data (recovery, calibration, precision for at least >=3 samples at LOQ) are required.
- Acceptable techniques e.g. GC-MS & LC-MS⇔2 additional ions; MS/MS detection⇔2 additional transitions; GC⇔HPLC; GC-MS⇔GC-ECD; LC-MS⇔LC-UV…

*Update for biocides is necessary!*
Multi-residue methods for biocides?

TNsG on Data Requirements: “In principle, residue methods proposed should be multi-residue methods, a standard multi-residue method should be assessed and reported…”

- DFG S19 and QuEChERS method for pesticides
- Applicability for soil, water(?)

- for drinking water samples: direct injection with LC-MS/MS separation and detection

- direct injection applicable e.g. for bendiocarb, cyproconazole, dichlorvos, fenoxacarb, imidacloprid, metofluthrin, pyriproxifen, tebuconazole, thiamethoxam, thiacloprid (regulated as pesticides + biocides)
Summary and Conclusion (1)

- Clear rules to define the minimum scope of methods (which matrices?) are needed.
- PT based definitions are necessary identifying for which matrices residue analytical methods are indispensable.
- Generally acceptable waiving arguments should be discussed instead of numerous case-by-case decisions.
- The residue definition should be generally discussed by toxicological and ecotoxicological experts during the EU assessment and published in the Assessment Report.
- The requirements for the validation of analytical methods for biocides should be updated.
- Clarification about validation of confirmatory methods required!

Job for ECHA and Competent Authorities
Summary and Conclusion (2)

- Identification of high priority data gaps.
- Collection of data about validated multi-residue methods for environmental matrices.

Job for monitoring labs
Thank you for your attention

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What’s more up to date for pesticides?

- Analytical techniques no longer commonly available:
  - GC with packed columns
  - LC-LC column switching
  - Electrochemical detectors for HPLC and ion pair chromatography

- Additional analytical techniques considered commonly available now:
  - GC-HRMS
  - GC-MS/MS
  - GC-MS\textsuperscript{n}
  - LC-HRMS (+ LC-MS)