Nitrofurans as an example - How to control zero tolerance?

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The Situation

- Council Regulation (EC) No. 2377/90, Annex IV:
  - Pharmacologically active substances for which no Maximum Residue Limits (MRLs) are fixed
  - No ADI due to their nature of toxicity or a lack of data
  - No safe limit, unacceptable at any concentration

→ Accepted to reach a ban
→ Controled with zero-tolerance
Zero-Tolerance

What does zero-tolerance mean?

→ The respective residue should not be detectable
→ ‘Not detectable‘ is based on the limit of detection (LOD)

- Nowadays: LOD has decreased drastically
- Significance of regulations must sometimes be questioned in regard to the toxicity of residues determined in the lower ppb-level
Zero-tolerance

Basic Hypothesis of the zero-tolerance concept:
‘Residues of pharmacologically active substances in food of animal origin are a side-effect of the use of medicines in food producing animals’

Anti-Thesis:
A concentration level above ‘zero’ could be caused by other sources than the use of medicines in food producing animals
Possible other sources

- Cross contamination from former use
- Cross contamination from use in human medicine
- Environmental contamination
- Natural occurrence / formation

→ Limitation of a zero-tolerance concept, which arises from the progress of analytical instrumentation has to be discussed
Nitrofurans as an example

Nitrofurans:

- Banned within the EU in the 90th (zero-tolerance)
- Control was limited by the analytical technique
  - Abuse of nitrofurans was not possible to control adequate

Nowadays:

- Technical development in LC/MS-MS lowered LODs for nitrofuran metabolites for more than 4 orders of magnitude
- Minimum Required Performance Limits (MRPLs) for nitrofurans were set to 1 µg/kg according to Commission Decision 2002/657/EC
Semicarbazide
– more than a nitrofuran metabolite

Semicarbazide (SEM):

- Characteristic marker of the nitrofuran nitrofurazone
  → Zero-tolerances for SEM in food products

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\begin{align*}
\text{nitrofurazone} & \quad \text{SEM} \\
O_2N & \quad O \\
\end{align*}
\]

- Toxicological studies of SEM:
  Weak mutagenic activity, mainly in the absence of a metabolic activating system (EFSA, 2003)
Further possible sources for SEM in food products:

- **Azodicarbonamide (ADC)**
  - Identification of SEM in food packaged in glass jars with metal lids sealed with plastic gaskets that are foamed using the blowing agent ADC (EFSA, July 2003)
  - Identification of SEM in flour to which ADC was added as an improver (Pereira et al., 2004)

- **Hypochlorite Treatment**
  - Identification of SEM in carrageenan (E 470a) due to a bleaching step using hypochlorite (Hoenicke et al., 2004)
Semicarbazide
– more than a nitrofuran metabolite

Further possible sources for SEM in food products:

- Heat treatment
  - Identification of SEM in egg white powder due to a pasteurisation step (Gatermann et al., 2004)

- Natural occurrence
  - Identification of SEM in dried marine products (crayfish, algae) (Saari et al., 2004, Hoenicke et al., 2004)
Consequences for SEM testing

- November 2003, Community Reference Laboratory (CRL), Fougères:
  ‘Illegal use of nitrofurazone can be detected by targeting the bound residues of SEM’
  but: SEM from other sources was also shown to rapidly be bound

- December 2004, Standing Committee on the Food Chain and Animal Health (SCFCAH):
  ‘SEM in the animal fraction of composite food may arise from the use of nitrofurazone in live animals, but may also result from other sources or chemical reactions during processing’
  → Appropriate statement in the analytical test report in the case of positive SEM results in composite food products
Harmonised EU regulation of zero-tolerances

- The MRPL corresponds to the average limit above which the detection of a substance or its residues can be construed as methodologically meaningful

- Introduction of 'action limits'

- MRPLs shall be used as reference points for action
  - Only test results at or above the MRPL shall be considered non-compliant with Community legislation
  - Residues below the MRPL should be construed as not of immediate concern
Commission Decision 2005/34/EC – Ongoing problems

- MRPLs shall be used as reference points for action irrespective of the matrix tested

→ For control of nitrofurazone abuse possible other sources must be considered, especially in the case of composite and processed food!
Conclusion

- Introduction of MRPLs as *action limits* is the only acceptable compromise to deal with Annex IV compounds.
- Use of MRPLs as *action limits* for all matrices without any prove is not possible especially in the case of composite or processed food products.