



Nitrofurans as an example - How to control zero tolerance?

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- **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**
- **Controlled with *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

- **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

- 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:

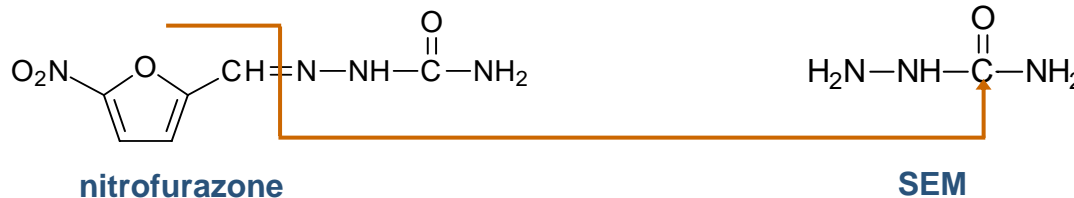
- Banned within the EU in the 90th (*zero-tolerance*)
- Control was limited by the analytical technique
 - Abuse of nitrofurans was not possible to control adequate
- Nowadays:
 - Technical development in LC/MS-MS lowered LODs for nitrofuran metabolites for more than 4 orders of magnitude
 - Minimum 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



- 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)

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)

- **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**



– 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!**

- 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