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**SANA BOLOGNA 2018**
**Botanicals and contaminants: emerging issues or new managing of existing risks?**

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# Contaminants in Food Supplements

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1. Legislation and principles
2. The process for setting maximum levels
3. Case studies
   - Pyrrolizidine alkaloids
   - 3-MCPD
4. Challenges
5. Conclusions

# 1. Legislation and principles

# EU Regulations Applicable to Food Supplements

## General Food Law
Reg EC 178/2002

General food safety requirements
Manufacturer responsibilities
Notification duty / Recall

## Food Supplements
Dir 2002/46/EC

Definition
Permitted forms and maximum levels (vit/ min)
Labeling

## Food Hygiene
Reg EC 852/2004

Rules for hygienic production based on the principles of HACCP
Microbiological criteria

## Labelling
Reg 1169/2011

How to label content, composition, etc
Allergen labelling

## Novel Foods
Reg EU 2015/2283

Pre-marketing approval procedure for novel ingredients


## Health Claims
Reg EC 1924/2006

Pre-marketing approval procedures for nutrition and health claims

## Fortification
Reg EC 1925/2006

Risk assessment and risk management procedure in case the use of a substance would result in harmful effects

## Additives
Reg EC 1333/2008

Pre-marketing approval procedures
Allowed additives
Conditions of use

## Pesticides residues
Reg EC 396/2005

Maximum residue levels

## Extraction solvents
Dir 2009/32/EC

Permitted extraction solvents

## Contaminants
Reg EC 1881/2006

Maximum levels of selected contaminants in ingredients that can be used in foods

## Irradiation
Dir 1999/2/EC

Permitted ingredients to be irradiated

# EU Contaminants Legislation

## Regulation 315/93

Covers agricultural and environmental contaminants.

> Does not apply to contaminants which are the subject of more specific legislation (e.g. pesticide residues, veterinary drug residues, ...).

Food containing a contaminant in an amount unacceptable from public health viewpoint shall not be placed on the market.

Contaminant levels shall be kept **as low as can reasonably be achieved (ALARA)**, following recommended good working practices.

Maximum levels must be set for certain contaminants to protect public health.

Sampling and methods of analysis (incl. detection limits) may be specified.

Consultation of EFSA before maximum levels are set.

Regulatory decisions by the Standing Committee on Plants, Animals, Food and Feed (PAFF).

# EU Contaminants Legislation

## Regulation 1881/2006

Establishes maximum levels for

- Nitrate
- Mycotoxins (Aflatoxins, Ochratoxin A, Patulin, Deoxynivalenol, Zearalenone, Fumonisins, T-2 and HT-2 toxin, **Citrinin**, Ergot sclerotia and ergot alkaloids)
- Heavy metals (**Lead**, **Cadmium**, **Mercury**, Tin, Arsenic)
- 3-monochloropropanediol (3-MCPD) and glycidyl fatty acid esters
- Dioxins and PCBs (Benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene)
- **Polycyclic aromatic hydrocarbons**
- Melamine and its structural analogues
- Inherent plant toxins (Erucic acid, Tropane alkaloids)

Under discussion

- Pyrrolizidine and Ergot alkaloids
- 3-MCPD for fish oil
- Perchlorate

# EU Contaminants Legislation

## Regulation 1881/2006

| | Foodstuffs (1) | Maximum levels (mg/kg wet weight) |
|---|---|---|
| 3.1 | Lead | |
| 3.1.22 | Food supplements (39) | 3,0 |
| 3.2 | **Cadmium** | |
| 3.2.21 | Food supplements (39) excl. food supplements listed in point 3.2.22 | 1,0 |
| 3.2.22 | Food supplements (39) consisting exclusively or mainly of dried seaweed, products derived from seaweed, or of dried bivalve molluscs | 3,0 |
| 3.3 | **Mercury** | |
| 3.3.3 | Food supplements (39) | 0,10 |

(39) The maximum level applies to the food supplements as sold.

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# EU Contaminants Legislation

## Regulation 1881/2006

| Foodstuffs | | Maximum levels (µg/kg) | |
|---|---|---|---|
| 6.1 | Benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene | Benzo(a)pyrene | Sum of benzo(a)-pyrene, benz(a)an-thracene, benzo(b)flu-oranthene and chry-sene ([45]) |
| 6.1.13 | Food supplements containing botanicals and their prepara-tions ([39]) (*******) (********)<br><br>Food supplements containing propolis, royal jelly, spirulina or their preparations ([39]) | 10,0 | 50,0 |

([39]) The maximum level applies to the food supplements as sold.

(*******) Botanical preparations are preparations obtained from botanicals (e.g. whole, plant parts, fragmented or cut plants) by various processes (e.g. pressing, squeezing, extraction, fractionation, distillation, concentration, drying up and fermentation). This definition includes comminuted or powdered plants, plant parts, algae, fungi, lichen, tinctures, extracts, essential oils (other than the vegetable oils referred to in point 6.1.1), expressed juices and processed exudates.

(********) The maximum level does not apply to food supplements containing vegetable oils. Vegetable oils used as an ingredient in food supplements should comply with the maximum level established in point 6.1.1. ◄

# EU Contaminants Legislation

## Regulation 1881/2006

| | Foodstuffs (1) | Maximum levels (µg/kg) |
|---|---|---|
| 2.8 | **Citrinin** | |
| 2.8.1 | Food supplements based on rice fermented with red yeast *Monascus purpureus* | 2 000 (*) |

(*) The maximum level is to be reviewed before 1 January 2016 in the light of information on exposure to citrinin from other foodstuffs and updated information on the toxicity of citrinin in particular as regards carcinogenicity and genotoxicity. ◄

# Dilution and concentration factors

## Regulation 1881/2006

Provides for the possibility to apply **dilution or concentration factors** for foods that are dried, diluted, processed or composed of more than one ingredient

(provided no specific limits are set for such commodities).

Must be taken into account:

- Changes of the concentration of the contaminant caused by drying or dilution processes;
- Changes of the concentration of the contaminant caused by processing;
- The relative proportions of the ingredients in the product;
- The analytical limit of quantification.

The specific factor shall be provided and justified by the operator

If not or the authority deems that factor inappropriate, the authority shall itself define that factor, based on the available information and to protect human health

# Prohibition of mixing and detocification

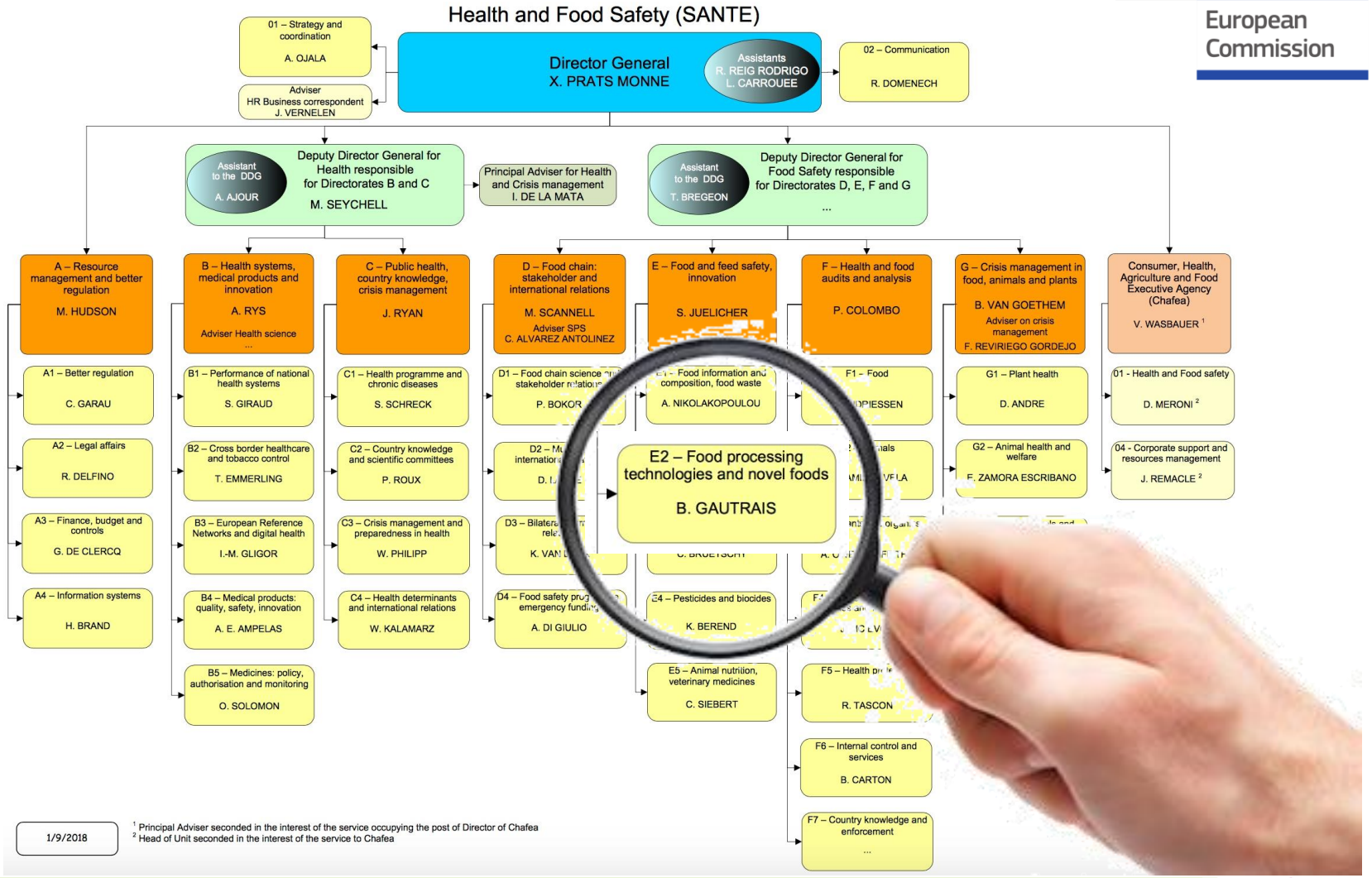
## Regulation 1881/2006

### Prohibits use, mixing and detoxification

- Foodstuffs not complying with the maximum levels must not be used as food ingredients.
- Foodstuffs complying with the maximum levels shall not be mixed with foodstuffs which exceed these maximum levels.
- Foodstuffs to be subjected to sorting or other physical treatment to reduce contamination levels shall not be mixed with foodstuffs intended for direct human consumption or with foodstuffs intended for use as a food ingredient.
- Foodstuffs containing containing mycotoxins shall not be deliberately detoxified by chemical treatments.

# 2. The Process

# The process




European Commission

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# The process


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European Commission

Discussion with Member States In EC working group

efsa
EFSA Journal

Call for data

Monitoring
Guidance levels
Action levels
Legal limits

Proposal for discussion

Consultation/ discussion with stakeholders

Inter-service consultation

PAFF COMMITTEE Adoption

Final proposal

Feedback Mechanism

# The role of EFSA

## Risk assessment of contaminants

Based on available data (mostly from official controls)

Establishing a health-based guidance Value (HBBGV, based on:

- Benchmark Dose Lower Confidence Limit (BMDL)
- No Observed Adverse Effect Level (NOAEL)

Which is either

- Tolerable Daily Intake value (TDI)
- Acute Reference Dose (ARfD)
- Tolerable Weekly Intake value (TWI)

→ Exposure below such values does not pose an appreciable risk to human health

Substances with genotoxic/carcinogenic potential or insufficient data

- No threshold dose for an effect can be identified
- Margin of Exposure approach (MOE), based on $BMDL_{10}$
- Threshold of Toxicological Concern approach (TTC), based on generic human exposure threshold values

# 3. Case Studies

# Pyrrolizidine alkaloids

Jan 2007: EFSA opinion related to PA as undesirable substance in feed

Nov 2011: EFSA opinion on PA in food and feed

- evaluation of the toxicity of PA for humans
- assessment of the relevance for the monitoring of PAs in food
- exposure of the EU population to PA, including specific groups of the population

1,2-unsaturated PAs are genotoxic and carcinogenic: no TDI but MOE

Possible health concern for toddlers and children who are high consumers of honey

Acute and chronic risk for supplements prepared from PA-containing plants

Collect analytical data on occurrence of PAs, including in milk, eggs and meat

Oct 2012: Draft EMA statement on the use of drugs containing PAs

PAs could be regarded as both hepatotoxic and carcinogenic

Herbal medicinal products containing herbal preparations with PAs (even in very low amounts) should not be used orally

Pregnant and nursing woman and children/adolescents should be excluded from the usage of products containing toxic, unsaturated PAs (even in very low amounts)

# Example: Pyrrolizidine alkaloids

Jul 2013: BfR press release: Levels of PA in herbal teas/teas are too high

Efforts are required to lower PA in herbal teas/teas to the greatest possible extent

Need for adequate checks of PA levels in batches and research into the cause of high PA

Nov 2013: 2nd EMA statement

Max limit: 0.35 µg/d (0.014 µg/d children)

Oct 2014: DGCCRF survey to collect data on honey and food supplements

84 samples (53 honeys and 31 food supplements). One third of the samples of food supplements were at levels between 2.3 and 225 mg/kg

The levels of pyrrolizidine alkaloids would not lead, by sole consumption of the food commodity, to exceed the exposure level inducing a long-term toxic effect (15 µg/kg BW/d)

May 2015: RIVM: maximum level for PA in herbal tea and preparations

Maximum level for PA in herbal preparations (including food supplements) should be 1 µg/kg

The level is adequate and could be increased to 5 µg/kg for herbal tea and herbal food supplements

# Example: Pyrrolizidine alkaloids

Aug 2015: EFSA: report on Occurrence of PAs in food

By RIKILT (NL), BfR (DE) and IRTA (ES) to obtain representative data on PA in Europe

Jul 2016: EFSA: Dietary exposure assessment to PAs in the EU population

Jun 2017: EFSA Risks for human health related to the presence of PAs

Possible health concern for toddlers and children who are high consumers of honey

Possible concern for frequent and high consumers of tea and herbal infusions

Consumption of food supplements based on PA-producing plants could result in exposure levels causing acute/short-term toxicity

17 PAs are of relevance for monitoring in food and feed

2017-2018: EC discussions on setting maximum levels

For Tea and Herbal Infusion

For Food Supplements

For Honey

# Example: Pyrrolizidine alkaloids

## Food Supplements Europe Activities

- Collection of analytical data
- Scientific and regulatory comments
  - Differentiating between PA producing plants and adventitious contamination
  - Highlighting the practical difficulties of PA management
  - Promoting of the Codex Code of Practice for weed control to prevent and reduce pyrrolizidine alkaloid contamination in food and feed' (CAC/RCP 74-2014)
  - Highlighting the problems with analytical methodology
  - Stressing the need for sufficient time to implement the measures
- Discussions with the European Commission
- Alignment with other sectors

# Example: 3-MCPD in Fish Oil

Dec 2007: BfR assessment (Infant formula and follow-up formula may contain harmful 3-MCPD fatty acid esters)

Mar 2016: EFSA: Risks for human health related to 3- and 2-monochloropropanediol (MCPD), and their fatty acid esters, and glycidyl fatty acid esters in food

- 3-MCPD is formed when refined vegetable oils are heated to high temperatures
- The highest levels are found in palm oils and palm fats, but also in other oils and fats
- Tolerable daily intake (TDI) of 0.8 µg/kg BW/d for 3-MCPD
- Exposures to 3-MCPD for age up to 18 years exceeds the TDI
- Foods contributing include pastries, potato crisps, shortcut pastry and cookies

Apr 2016: RIVM: Preliminary assessment of exposure to 3-MCPD in NL

- 18% of children exceed safe level

Nov 2016: JECFA: COMMITTEE ON FOOD ADDITIVES

- Tolerable Daily Intake for 3-MCPD of 4 µg/kg BW/d (five times higher than EFSA)

# Example: 3-MCPD in Fish Oil

Jan 2017: EC: information on the presence of 3-MCPD in fish oil

- Based on 2 publications
- Call for data
- **FSE** aligned with GOED (Global Organization for EPA and DHA Omega-3) to submit data

Feb 2017: EC

- No intention to set max levels in fish oil. Recommendation to monitor.

Nov 2017: EFSA: Update of the risk assessment on 3-MCPD and its esters

- Updated group TDI of 2 µg/kg BW/d
- TDI is not exceeded in the adult population. Slight exceedance of the TDI in the high consumers of the younger age groups and in particular infants receiving formula

Apr 2018: EC: discussions ongoing

- Based on Codex Alimentarius discussions
- GOED data show and suggest that MLs for vegetable oil could be used for fish oil
- **FSE** provided updated data to Commission

# Challenges

## 1. Availability of data

Data are essential to be able to discuss

- Both EC and EFSA launch calls for data

FSE calls for data (anonymised)

- Content
- Use levels
- Analytical details (method, LoD, LoQ)

EC/EFSA use multiple sources of data

- National monitoring data
- Official controls data
- Industry data

Providing data is essential for being in the discussion

# Challenges

**2. Methods of analysis**

In many cases no official methods exist

Levels proposed are not measurable, except by specialised labs

Measurements are often unreliable

*e.g. PAH (polycyclic aromatic hydrocarbons)*

| | |
|---|---|
| *June 2012:* | *Technical Workshop on PAH to discuss the technical challenges related to PAH testing in food supplements* |
| *Sep 2014:* | *Discussions start because of findings of high levels* |
| | *Call for data* |
| | *FSE Stressed the methodological constraints* |

# Challenges

## 2. Methods of analysis

Sample was sent to five European contract laboratories with a request for the results to be reported as the sum of the four substances (PAH4).

The results are as shown below:

Sum of PAH 4 reported by the 5 laboratories

| | µg/g |
|---|---|
| Laboratory 1 | 105.83 |
| Laboratory 2 | 325.00 |
| Laboratory 3 | 17.00 |
| Laboratory 4 | 209.30 |
| Laboratory 5 | 107.60 |

Analyses for the individual substances from the laboratory ring trial gave the following ranges (µg/g).

| | | | |
|---|---|---|---|
| Benzo(a)pyrene | <1.00 | to | 65.00 |
| Chrysene | <4.00 | to | 130.00 |
| Benzo(a)anthracene | 10.00 | to | 70.00 |
| Benzo(b)fluoranthene | <2.00 | to | 60.66 |

# Challenges

**3. Practicalibility**

Unavoidable contaminants

*e.g. Pyrrolizidine alkaloids*

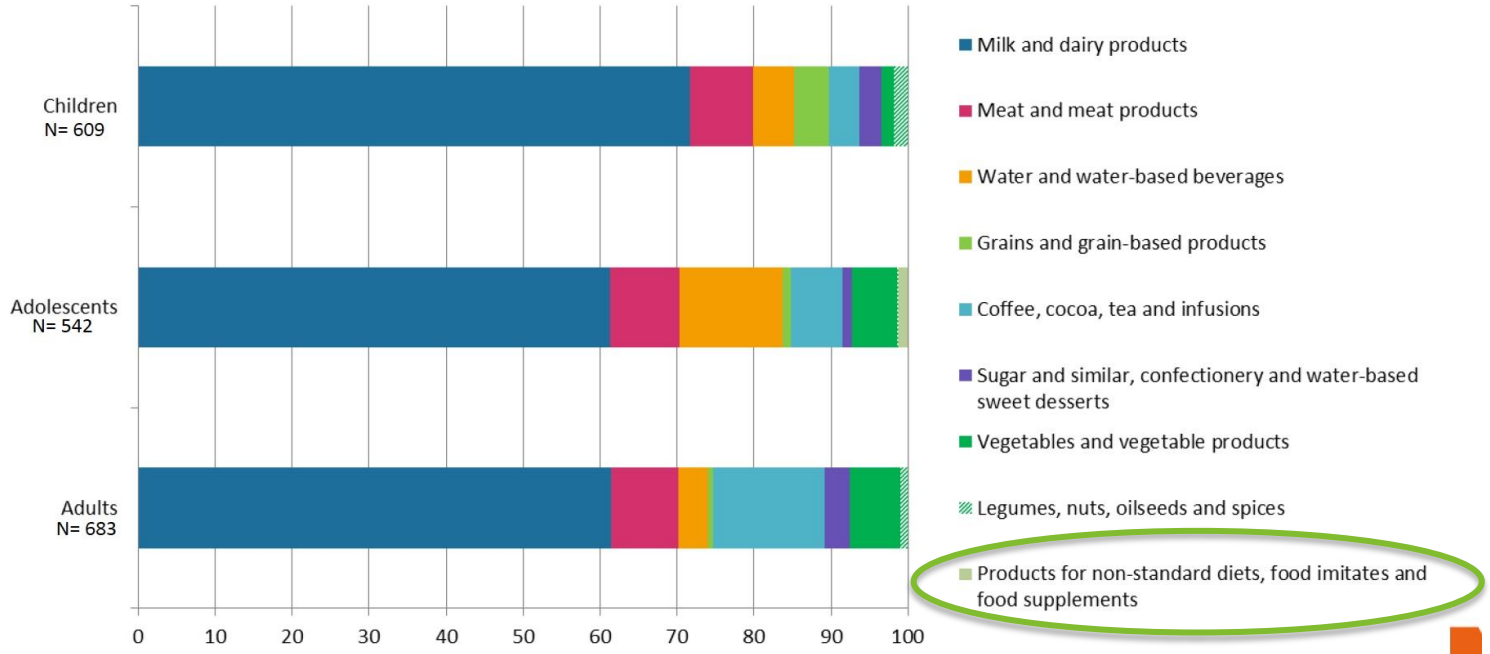
Adherence to guides

Sampling

Analytical issues

# Challenges

## Relative contribution of the different food groups to the total PAs intake (N=1834)




Lowest PAs concentration levels
Higher contributor to PAs intake

Highest PAs concentration levels
Lowest contributor to PAs intake

.be

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# Challenges

**4. Costs**

Any requirement requires systematic analysis that may not be necessary

*e.g. PAH*

*FSE succeeded to limit the requirements to botanicals*

*e.g. Perchlorate*

*The general limit will probably not be included in legislation*

Any requirement that is too strict results in higher rejection rate

Analysis requiring specialised labs increase costs substantially

# Challenges

**5. Approach also applies to other substances**

Hydroxyanthracene derivatives (HAD) containing plants

EFSA: HAD have genotoxic and carcinogenic effects

HAD are responsible for the beneficial health effect on gut function

EC proposes prohibition of the use of Aloe spp.

EMA continues to accept such products

Monakolin K

EFSA: Serious adverse effects are of health concern

# 4. Conclusions

# Conclusions

Contaminants are harmonised at EU level

Maximum levels are set based on the ALARA principle

Opinion of EFSA is essential (harmful effects / exposure)

Critical developments today include pyrrolizidine alkaloids and 3-MCPD

Challenges include analytical methods and costs

Data are essential

# Food Supplements Europe

## Food Supplements Europe Food Supplements Quality Package


GMP Guide

GMP Self Assessment Questionnaire


Botanical Preparations Guide

Botanical Preparations Self Assessment Tool

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# Thank You

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