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PhytoLab

Quality of Herbal Medicinal Products and Botanical Food Supplements – EU regulation and practical experience

59th International Congress and Annual Meeting of the Society for Medicinal Plant and Natural Product Research
4 – 9 September 2011, Antalya
Workshop III

Hartwig Sievers



Topics

1. Definitions
2. Overview of Quality Regulations
3. Quality and Safety
4. Conclusions



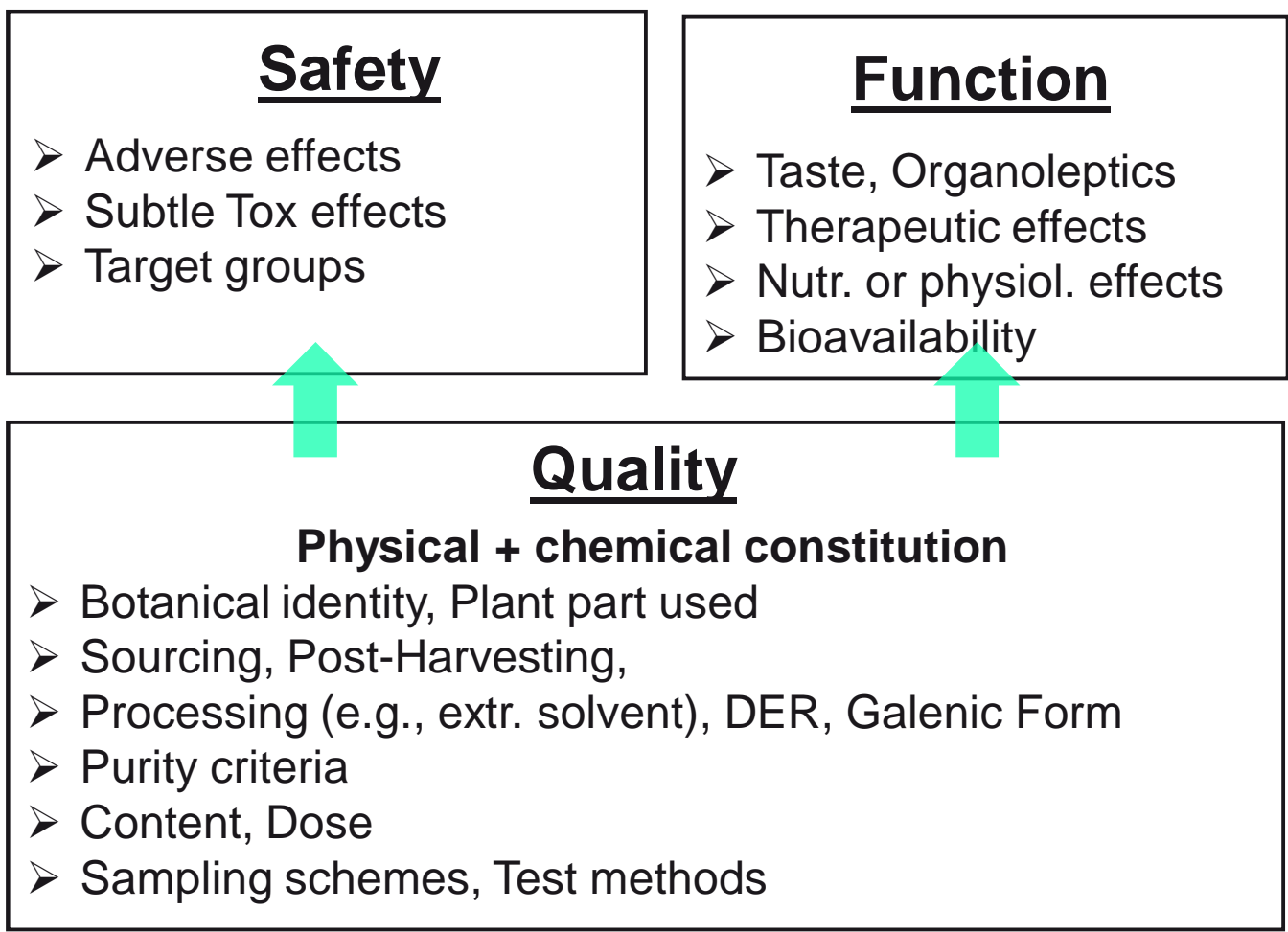
Definitions

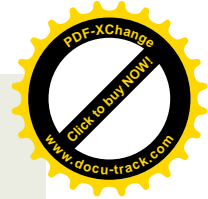
Quality (ISO 8402-1986)

“the totality of features and characteristics of a product or a service that bears its ability to satisfy stated or implied needs”

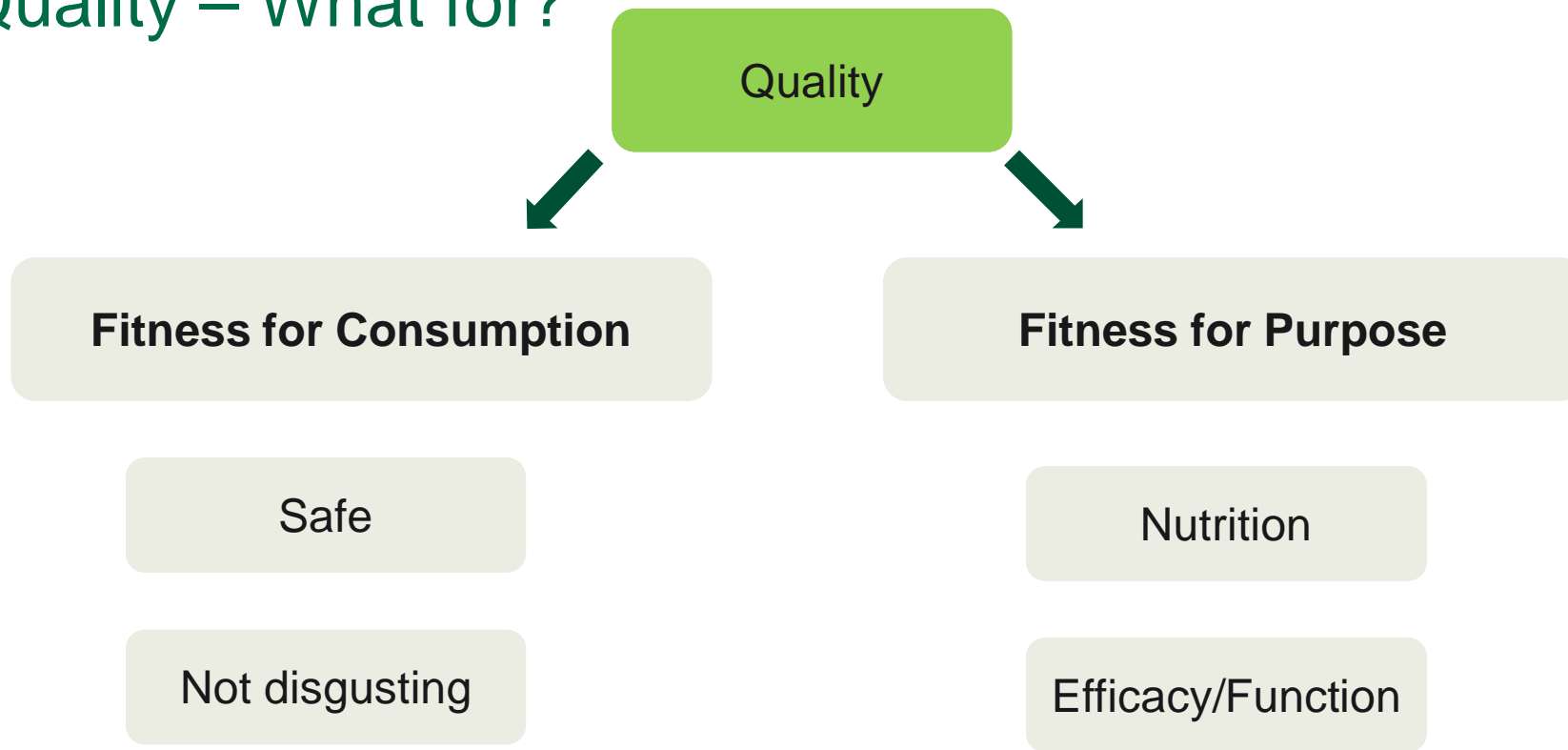


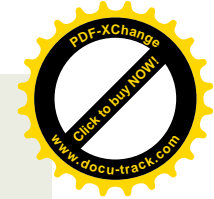
Safety and Function: Quality matters





Quality – What for?

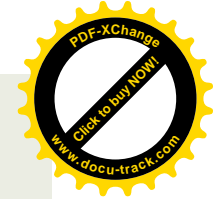




Quality – Herbal Medicinal Products

- Common standards
 - Sampling
 - Dosage Forms
 - Dissolution
 - Disintegration
 - ...
- Specific standards for HMP
 - Quality criteria (Microbiology, Heavy Metals, Pesticides...)
 - Methods (Heavy Metals, Aflatoxins...)
 - Monographs for Herbal raw materials and extracts (inc. Specifications and Methods for Identity, Purity, Assays)
 - *General Monographs „Herbal Drugs“, „Extracts“, „Herbal Infusions“...*





Quality – Herbal Medicinal Products

| | Chapter |
|---|---------|
| ➤ Pesticide residues | 2.8.13 |
| ➤ Determination of aflatoxin B ₁ in herbal drugs | 2.8.18 |
| ➤ Determination of ochratoxin A in herbal drugs | 2.8.22 |
| ➤ Heavy metals in herbal Drugs and Fatty Oils | 2.4.27 |
| ➤ Microbiological examination of herbal medicinal products for oral use | 2.6.31 |
| ➤ Microbiological quality of herbal medicinal products for oral use | 5.1.8 |
| ➤ Residual solvents | 2.4.24 |

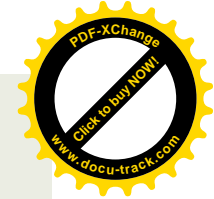


Quality – Herbal Medicinal Products

Directive 2004/24/EC (THMPD)

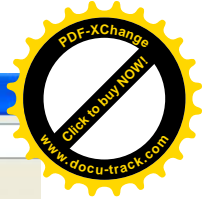
(5)

„The quality aspect of the medicinal product is independent of its traditional use so that no derogation should be made with regard to the necessary physico-chemical, biological and microbiological tests.“



Quality Guidelines – Herbal Medicinal Products (e.g.)

- **Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products** CPMP/QWP/2819/00 Rev. 1; EMEA/CVMP/814/00 Rev. 1; 30 March 2006
- **Reflection Paper on Stability Testing on Herbal Medicinal Products and Traditional Herbal Medicinal Products**; EMA/HMPC/3626/2009, 21 October 2010
- **Guideline on Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products**
CPMP/QWP/2820/00 Rev.1; EMEA/CVMP/815/00 Rev. 1; 30 March 2006
- **Note for Guidance on Validation of Analytical Procedures: Text and Methodology**
ICH Topic Q 2 (R1); CPMP/ICH/381/95; June 1995
- **Impurities: Guideline for Residual Solvents**
ICH Topic Q3C (R5); EMA/CHMP/ICH/82260/2006; March 2011
- **Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products**
CPMP/QWP/122/02, rev. 1 corr; 17 December 2003



- ▼ Human medicines
 - Pre-authorisation
 - Post-opinion
 - Post-authorisation
 - Product information
 - Scientific advice and protocol assistance
- ▼ Scientific guidelines
 - ▼ Quality
 - Active Substance
 - Manufacturing
 - Impurities
 - Specifications, analytical procedures and analytical validation
 - Excipients
 - Packaging
 - Stability
 - Pharmaceutical development
 - Specific types of products
 - Post approval

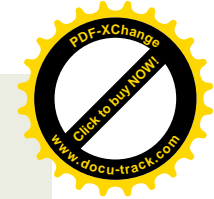
► Home ► Regulatory ► Human medicines ► Scientific guidelines ► Quality
► Specifications, analytical procedures and analytical validation

Quality: Specifications, analytical procedures and analytical validation

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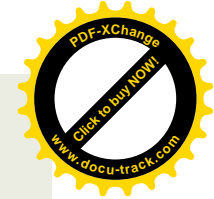
If you have comments on a document which is open for consultation, please use the Form for submission of comments on scientific guidelines.

| Topic | Documents | Reference number | Publication date | Effective date | Remarks |
|---|--------------------------------------|----------------------------|-----------------------------------|----------------|--------------------------------|
| ICH Topic Q8, Q9 and Q10 Quality Implementation Working Group Questions and Answers | Adopted guideline | CHMP/ICH/265145/09 | Dec 2009 | Dec 2009 | |
| Q 4B Annex 11 Capillary Electrophoresis General Chapter | Draft guideline | CHMP/ICH/730028/09 | Release for consultation Dec 2009 | | Deadline for comments Feb 2010 |
| Q 4B Annex 12 Analytical Sieving General Chapter | Draft guideline | CHMP/ICH/730808/09 | Release for consultation Dec 2009 | | Deadline for comments Feb 2010 |
| Q 4B Annex 9 Step 3 Tablet Friability General Chapter | Draft guideline | CHMP/ICH/379801/09 ICH Q4B | Release for consultation Jun 2009 | | Deadline for comments Sep 2009 |
| Q 4B Annex 10 Step 3 Polyacrylamide Gel Electrophoresis | Adopted guideline Draft guideline | CHMP/ICH/381133/09 ICH Q4B | Dec 2009 | May 2010 | |



Quality – Herbal Medicinal Products

- HMP quality is highly regulated and defined
- Elaboration of the quality dossier is the main cost driver and the major time factor in establishing marketing authorisations for (T)HMPs
- The elevated levels and narrow margins of quality standards for herbal raw materials impose a strong restraint on the choice of batches and sources



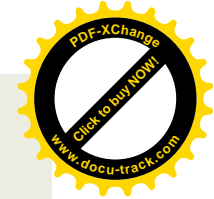
Quality – Botanical Food Supplements

Regulation (EC) No 178/2002

Article 8

Protection of consumers' interests

1. Food law shall aim at the protection of the interests of consumers and shall provide a basis for consumers to make informed choices in relation to the foods they consume. It shall aim at the prevention of:
 - (a) fraudulent or deceptive practices;
 - (b) the adulteration of food; and
 - (c) any other practices which may mislead the consumer.

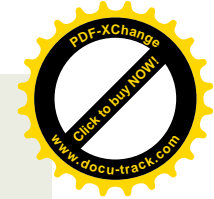


Quality – Botanical Food Supplements

Regulation (EC) No 178/2002

Article 14, Food safety requirements

1. Food shall not be placed on the market if it is unsafe.
2. Food shall be deemed to be unsafe if it is considered to be:
 - (a) injurious to health;
 - (b) unfit for human consumption.



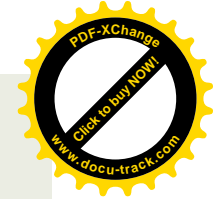
Quality – Botanical Food Supplements

Regulation (EC) No 178/2002

Article 14, Food safety requirements

3. In determining whether any food is unsafe, regard shall be had:

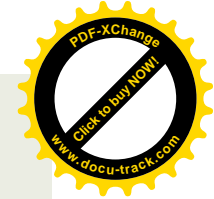
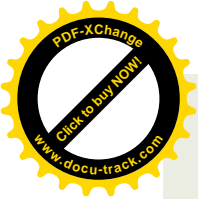
- (a) to the normal conditions of use of the food by the consumer and at each stage of production, processing and distribution, and
- (b) (b) to the information provided to the consumer, including information on the label, or other information generally available to the consumer concerning the avoidance of specific adverse health effects from a particular food or category of foods.




Quality – Botanical Food Supplements

- Pesticide residues Regulation (EC) 396/2005
- Metals * Regulations (EC) 396/2005 and Regulation (EC) 1881/2006
- Mycotoxins Regulation (EC) 1881/2006
- Contaminants others Regulation (EC) 1881/2006
 - PAH Regulation (EC) No 835/2011 amending 1881/2006
- Irradiation Directives 1999/2/EC and 1999/3/EC
- Solvents Directive 2009/32/EC
- Hygiene Regulation (EC) 852/2004 (HACCP)

* Apart from Heavy Metals the category of (Botanical) Food Supplements is not expressly addressed in these regulations



Quality – Botanical Food Supplements



European Food Safety Authority EFSA Journal 2009; 7(9):1249

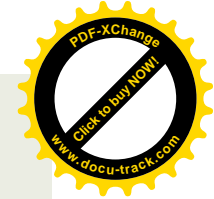
SCIENTIFIC OPINION

Guidance on Safety assessment of botanicals* and botanical preparations
intended for use as ingredients in food supplements¹**

EFSA Scientific Committee²

European Food Safety Authority (EFSA), Parma, Italy

This guidance document published on 9 September 2009, replaces the earlier version published on 20 June 2008 with the Question Number: EFSA-Q-2005-233.

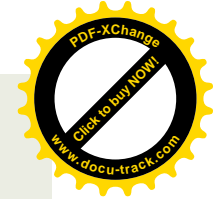


Quality – Botanical Food Supplements

Data requirements for the safety assessment of botanicals

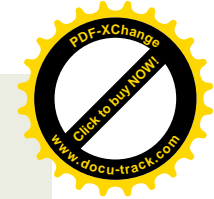
Technical data

- Identity and nature of the source material
- Manufacturing process
- Chemical composition
- Specifications
- Stability



Quality – Botanical Food Supplements

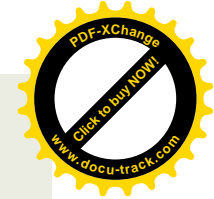
- ✓ Like for all food the producer is mainly responsible for defining a quality level that provides compliance with 178/2002/EC Art. 14
- ✓ Specific quality regulation applicable to BFS is in place for main purity criteria, e.g., contaminants or residual solvents
- ✓ No common harmonised basis for identity or adulteration of botanical raw materials or products, no common standard for „fitness-for-purpose“ criteria



Quality - Botanical Food Supplements

Industry Self-Regulation (examples)

- EHIA - European Herbal Infusion Association
Compendium of Guidelines for Herbal and Fruit Infusions and Products thereof
<http://www.ehia-online.org/publications.html>
- EBF - European Botanical Forum
<http://www.botanicalforum.eu/index.php?page=contact-us>
- EHPM - European Health Products Manufacturers
<http://www.ehpm.org/pdfs/8990EHPM%20Report%20for%20web.pdf>
- SYNADIET (France)
<http://www.synadiet.fr/synadiet/les-groupes-de-travail/gt-charte-de-qualite---details.html>
- ESA - The European Spice Association
<http://www.esa-spices.org/index-esa.html/publications-esa>



Quality - Botanical Food Supplements

other Quality Guidance Documents or Initiatives, e.g.,

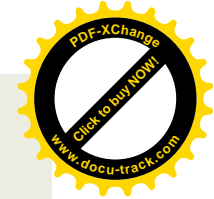
- AOAC

http://www.aoac.org/News/FDA_IDIQ.htm

- Health Canada

Evidence for Quality of finished Natural Health Products

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodnatur/eq-paq-eng.pdf



Quality and Safety

Identification

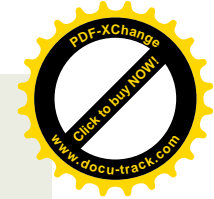
- macroscopic examination
- microscopic examination
- TLC

⇒ Purity

- foreign species
- foreign matter
- spiking, adulteration
- contaminants
- microbiology

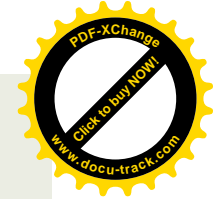
➤ Tests and Assay

- Loss on drying
- Total ash
- Assay (where applicable)
 - markers
 - active compounds
 - **limited compounds**
- Bulk density
- Particle-size distribution



Quality and safety

- Quality-related causes for unsafe botanicals
 - Adulteration or mix-up with toxic species/plant parts
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(with influence on level of toxicologically relevant compounds)
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Adulteration or mix-up of safe herbs with toxic species



Available online at www.sciencedirect.com



Phytomedicine

Phytomedicine 16 (2009) 72–84

www.elsevier.de/phymed

Suspected hepatotoxicity by *Cimicifugae racemosae rhizoma* (black cohosh, root): Critical analysis and structured causality assessment

Rolf Teschke*, Alexander Schwarzenboeck

Medical Department II, Klinikum Hanau, Teaching Hospital of the Johann Wolfgang Goethe University of Frankfurt/Main, Leimenstraße 20, D-63450 Hanau, Germany

38 out of 42 patients: no causal relationship established

4 patients: causal relationship possible

- 1 case: no valid evaluation possible due to lack of basic information
- 1 patient had an autoimmune hepatitis unrelated to BC
- 2 other ones obviously had a hepatic liver disease

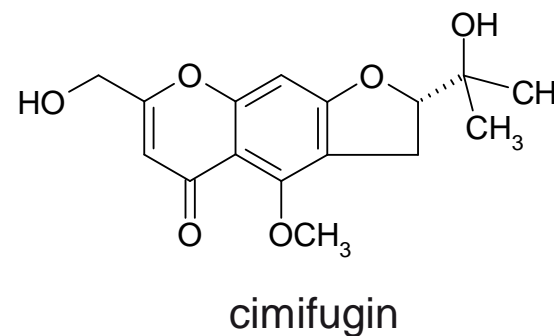
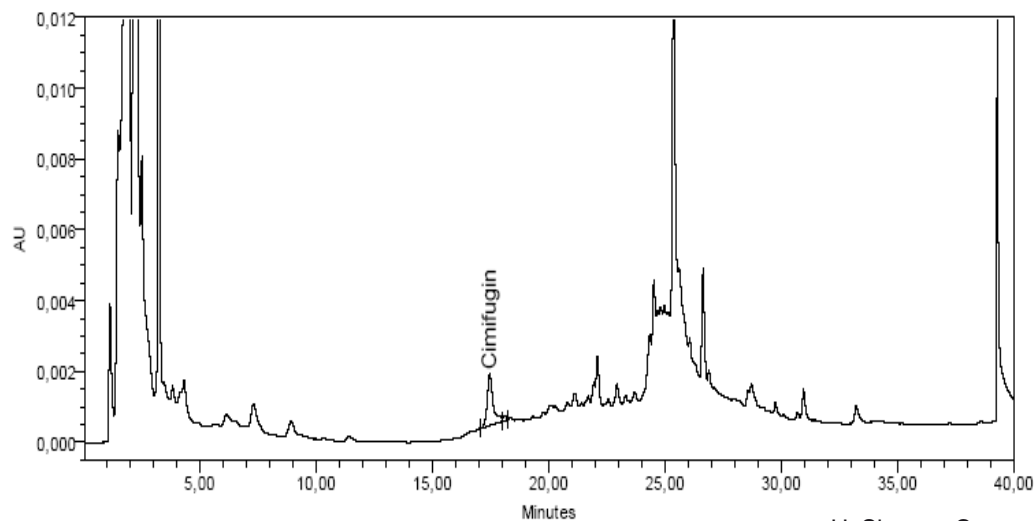
In some cases not *C. racemosa* but *C. foetida* was used

Adulteration or mix-up of safe herbs with toxic species

Cimicifuga racemosa: liver-toxic?

- Cimifugin is present in *C. foedita* and other *C.* species but not in *C. racemosa*
- Adulteration with *C. foedita* can be found by detecting the chromone cimifugin

2,5% *C. foedita* in *C. racemosa*



Adulteration of Star Anise with Shikimi Fruit

Illicium verum Hooker
Star anise

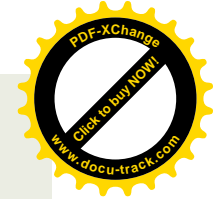
Illicium anisatum L.
(*religiosum* Sieb.)

Anisatin: ca. 10.2µg/ml; Scan 02
04050_002 131 (10.450) Sm (50, 200.90); Cm (129.133, 79.119+148.156)

I. verum, 4.5µg/ml

Anisatin

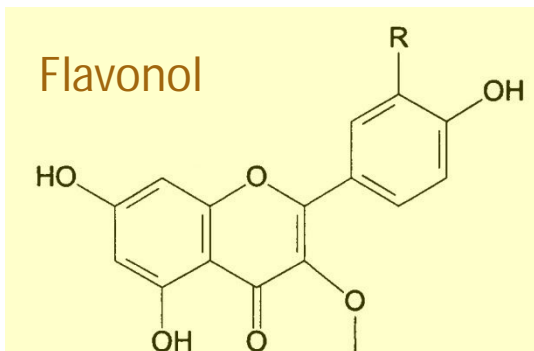
I. Lederer, K. Reif, J.-P. Steffen: ISOLATION OF ANISATIN AS REFERENCE SUBSTANCE FOR THE DETERMINATION OF TOXIC ADULTERATIONS IN ILLICIMUM VERUM BY HPLC-MS/MS ; ICNPR, Phoenix, 30 July-4 August 2004



Quality and safety

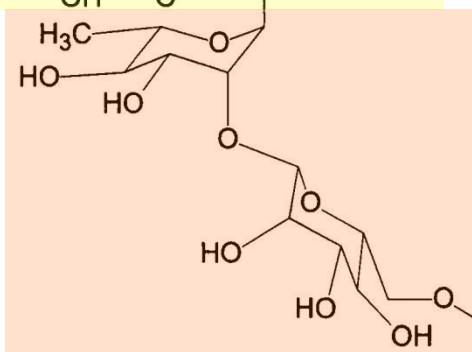
- Quality-related causes for unsafe botanicals
 - Adulteration or mix-up with toxic species/plant parts
 - **wilful admixture of chemical drugs, counterfeit extracts**
 - processing technology/galenic preparation
(with influence on level of toxicologically relevant compounds)
 - Contaminants (pesticides, mycotoxins, heavy metals, other)

Quality – adulteration of extracts

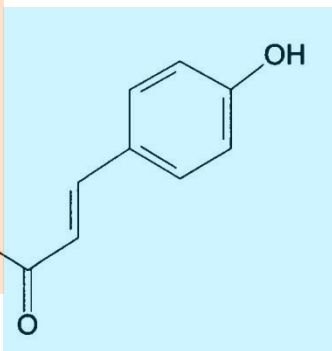


Ginkgo Flavone Glycosides

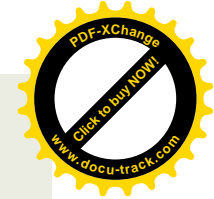
- R = H: Kaempferol
- R = OH: Quercetin MW: 302.2
- R = OCH3: Isorhamnetin



Diglycoside



Coumaroyl Ester



adulteration of extracts

e.g., Ginkgo biloba extracts

4 surveys in last 10 years with results indicating a progression of sophisticated adulteration

- Addition of rutin/quercetin from, e.g., buckwheat approx. \$10/kg
- *Fructus sophorae* additions to enhance Quercetin/Kaempferol ratio
- GBE cost \$ 35-90 / kg

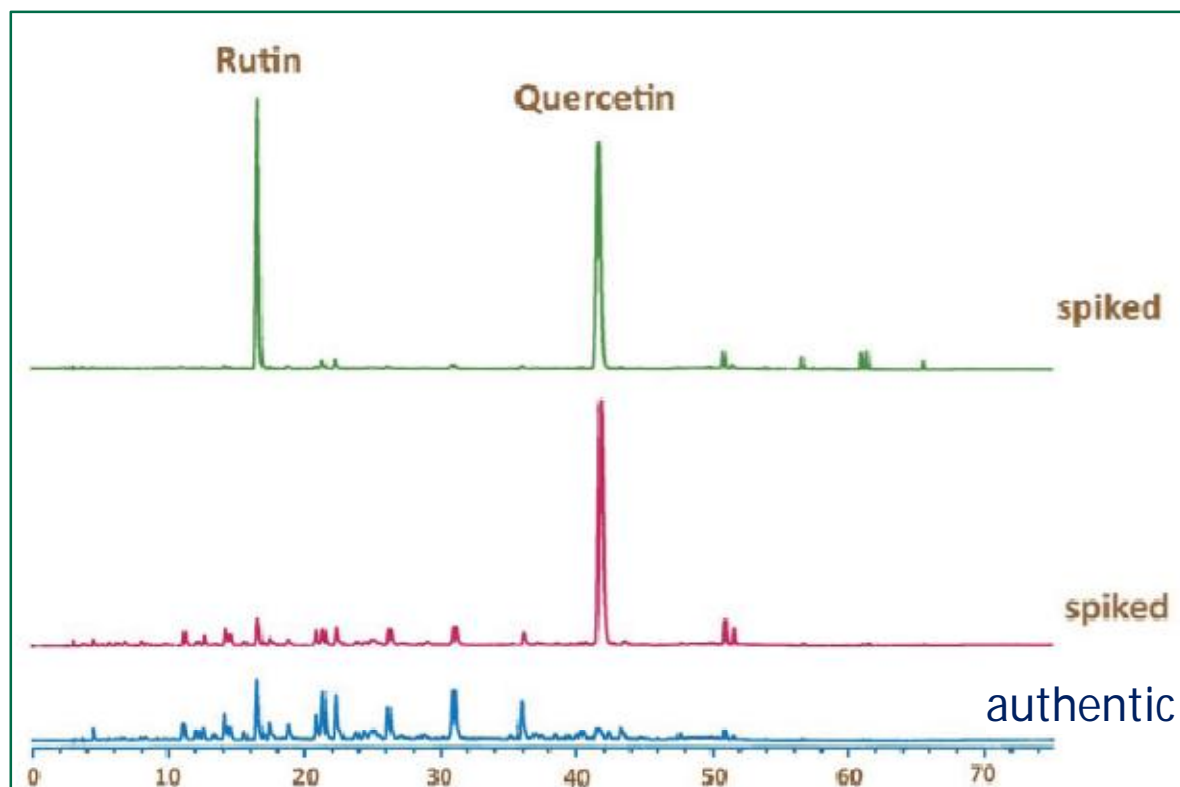
Literature:

Obermeyer, W.: *FDA Public Meeting on Economically Motivated Adulteration* , May 1, 2009

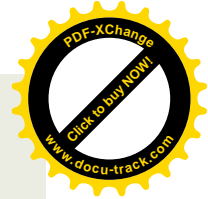
Tawab, M. et al, *Pharmazeutische Zeitung* 20; 2010

Quality - adulteration of extracts

Ginkgo



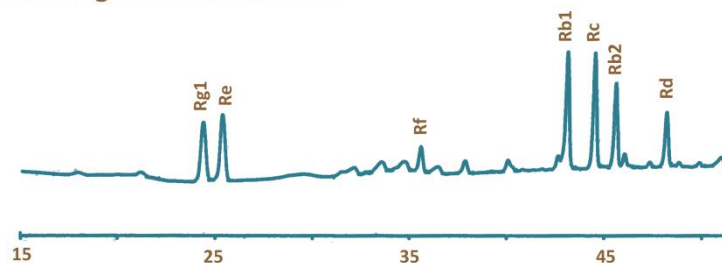
Roth-Ehrang, R.: 8th Annual Oxford International Conference on the Science of Botanicals;
Oxford, Mississippi, April 4-6, 2009



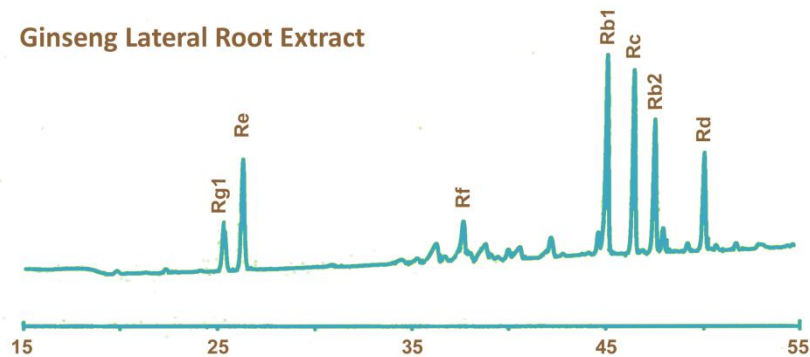
Quality - adulteration of extracts

Ginseng Comparison

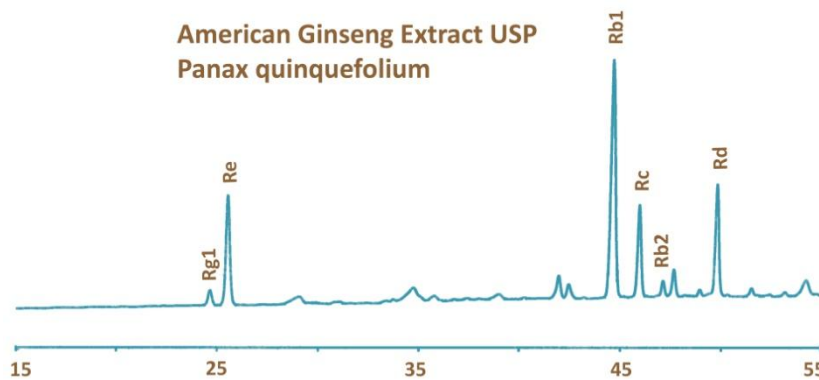
Ginseng Main Root Extract



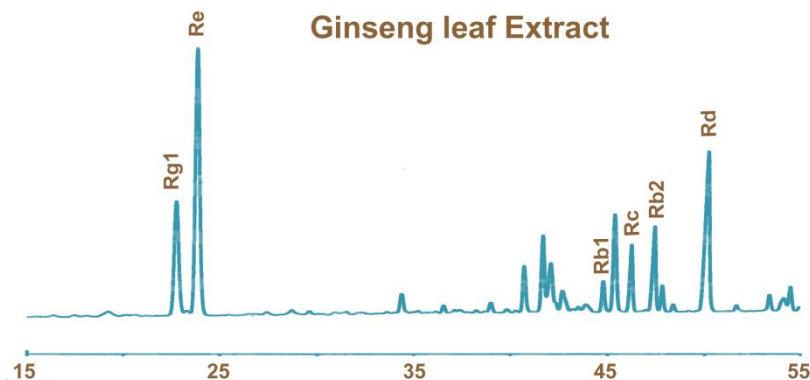
Ginseng Lateral Root Extract



American Ginseng Extract USP
Panax quinquefolium

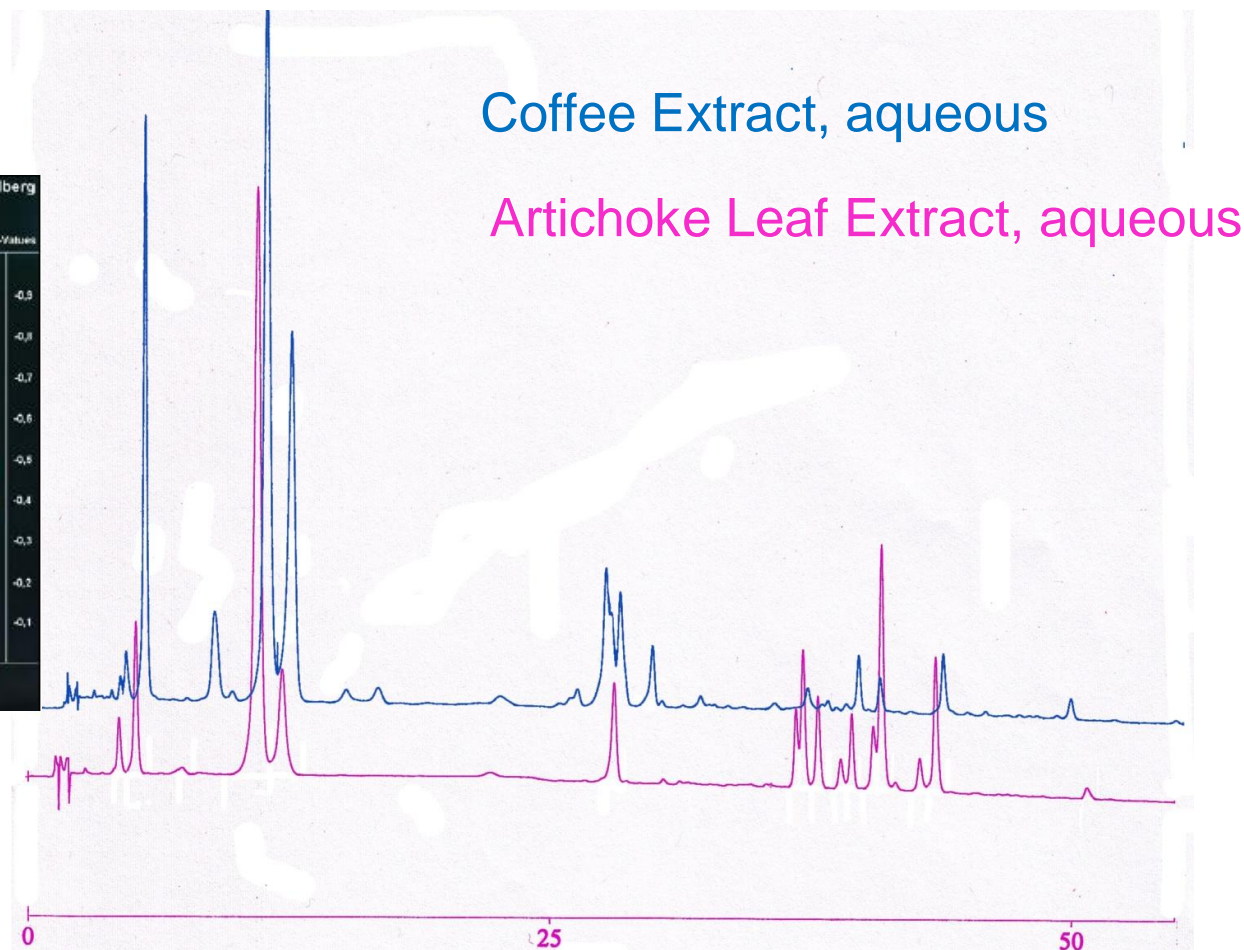


Ginseng leaf Extract



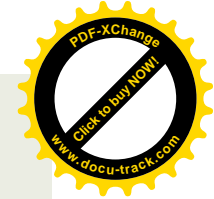
Quality - adulteration of extracts

Overlay



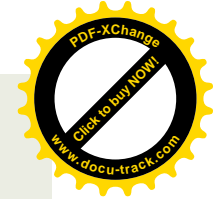
Coffee Extract, aqueous

Artichoke Leaf Extract, aqueous



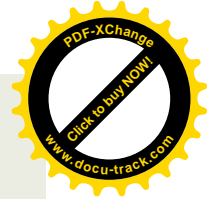
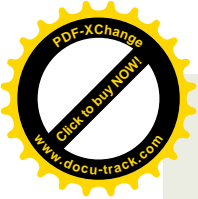
Quality and safety

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(with influence on level of toxicologically relevant compounds)
 - Contaminants (pesticides, mycotoxins, heavy metals, other)

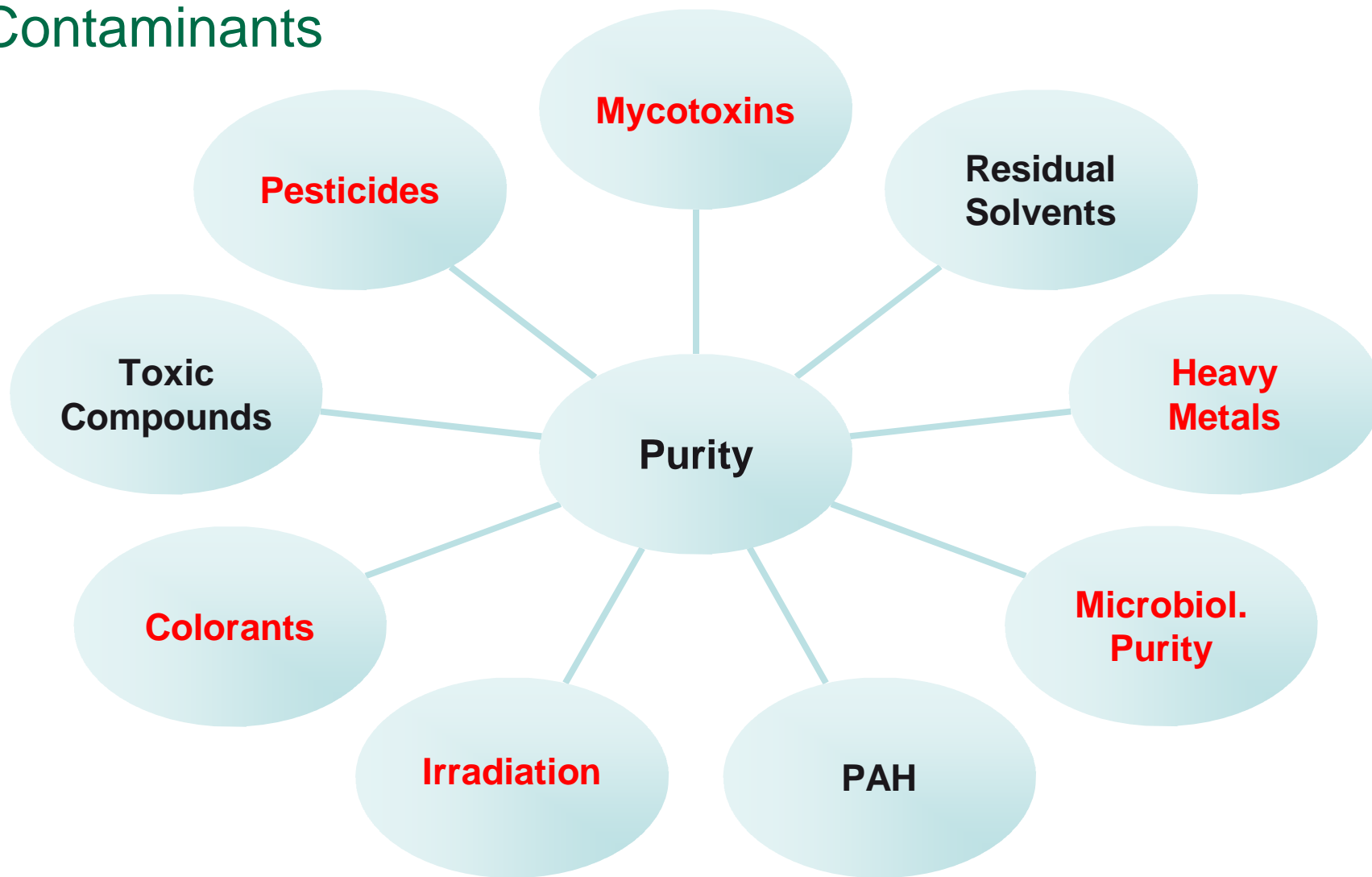


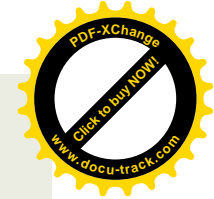
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Contaminants





Quality of botanicals

Contaminant

Regulation

Pesticides, Fumigants

Commission Directive 396/2005/EC as amended*

Mycotoxins

1881/2006/EC as amended*

Heavy Metals

1881/2006/EC as amended

PAH

1881/2006/EC as amended*

other (Dioxins, Nitrate, Furan ...)

1881/2006/EC as amended*

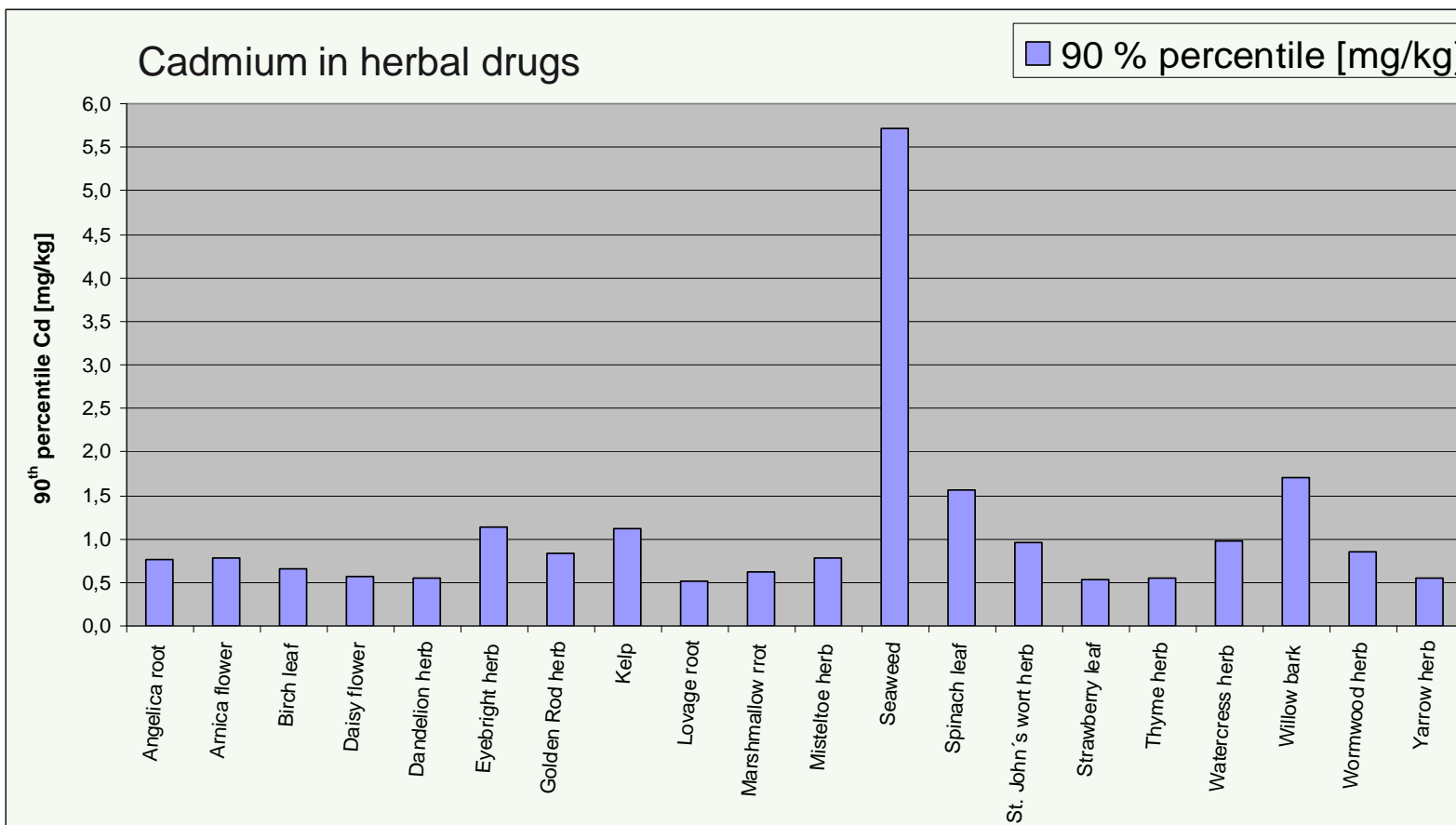
Microbial contamination

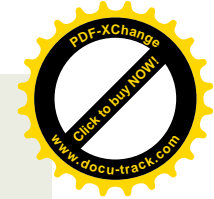
no limits regulated

*Apart from Heavy Metals the category of (Botanical) Food Supplements is not expressly adressed in these regulations



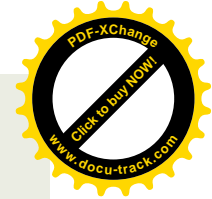
Contaminants



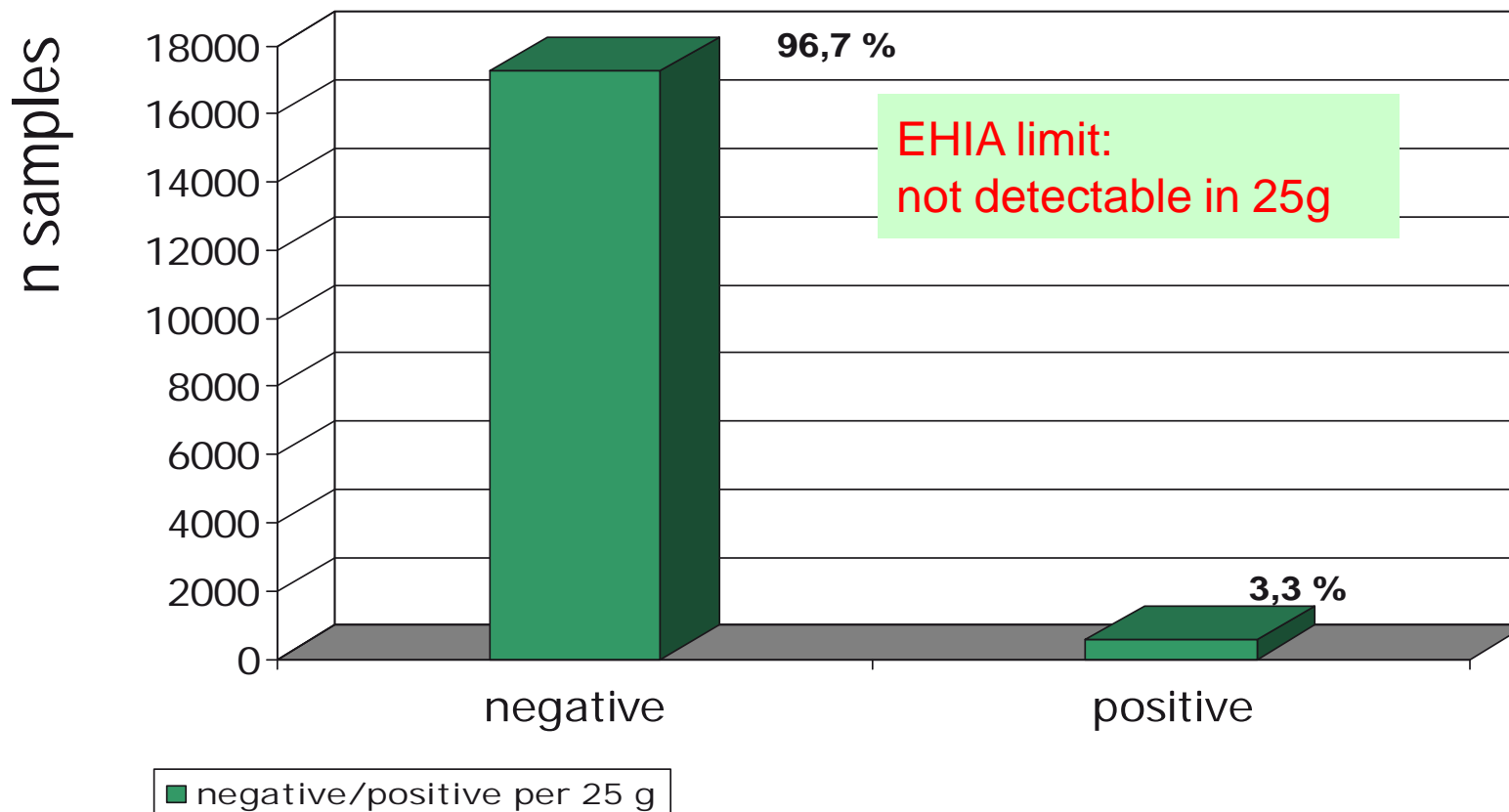


Irradiation

| Product | n | negative | positive | not assessable |
|---------------------|----|----------|----------|----------------|
| Garlic | 5 | 5 | - | - |
| Ginger | 12 | 5 | 3 | 4 |
| Santalum | 2 | 2 | - | - |
| Plantago husk | 3 | 3 | - | - |
| Ginseng | 12 | 9 | 1 | 2 |
| Herb- and Fruit Tea | 3 | 3 | - | - |
| Rhodiola Extract | 3 | - | 1 | 2 |
| Red Clover Extract | 25 | 14 | 10 | 1 |
| Soy Extract | 13 | 5 | 5 | 3 |



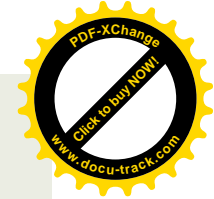
Salmonella in processed herbs (n = 17.833)





Quality – What for?





Conclusions

- ✓ Defined and controlled quality is an indispensable basis for safety and efficacy/function of both HMP and BFS
- ✓ Violation of existing regulatory quality standards is no prominent cause of safety concerns for BFS
- ✓ HMP standards are not 1 by 1 transferable to BFS but reference to certain Pharmacopoeial standards (identity, purity) would be an easy and efficient improvement
- ✓ For BFS with approved claims an adequate quality to ensure fitness for purpose needs to be defined



A safe situation is one where risks of injury are low and manageable.

<http://www.google.de/search?hl=de&q=wiki+safety&meta=>



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Thank You!

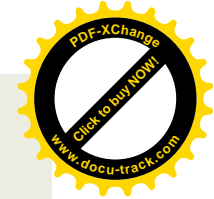
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Where do signals of potential risks come from?

| <u>Herb</u> | <u>suspected risk</u> | <u>source</u> |
|------------------------------------|-----------------------|----------------|
| <i>Piper methysticum</i> | liver toxicity | case reports |
| <i>Tussilago farfara</i> (+ other) | liver toxicity | case reports |
| <i>Cimicifuga racemosa</i> | liver toxicity | case reports |
| <i>Chelidonium majus</i> | liver toxicity | case reports |
| <i>Aristolochia spec.</i> | nephrotoxicity | case reports |
| <i>Ginkgo biloba</i> | bleeding | case reports |
| <i>Hypericum perforatum</i> | interactions | case reports |
| <i>Vaccinium macrocarpon</i> | interactions | case reports |
| <i>Cinnamomum cassia</i> | liver toxicity | animal studies |