

# Legal Requirements for the Control of Contaminants in Herbal Medicinal Products and Related Areas

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der Arzneimittel-  
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- ❖ Polycyclic aromatic hydrocarbons
- ❖ Plant protection products
  - Maximum residue limits
  - Approval/ authorisation of active substances/products
  - Integrated pest management

## Heavy Metals: European Pharmacopoeia

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- Monograph „Herbal drugs“ (draft „Extracts“)
  - Lead 5 mg/kg
  - Cadmium 1 mg/kg
  - Mercury 0.1 mg/kg
- Database of the BAH WG on Contaminants
- 7100 samples tested on Cd and Pb, 2002-2007
- Published\* with proposals for limits of 5 mg/kg for Pb and 0.5 mg/kg for Cd with certain exemptions

\* Gasser U, Klier B, Kühn AV, Steinhoff B. Pharmeuropa Scientific Notes 2009-1

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## Heavy Metals: European Pharmacopoeia

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Exemptions in individual monographs, e.g.

<b>Cd</b>	<b>Pb</b>
Fumitory 1.5 mg/kg	Nettle root (draft) 7.0 mg/kg
Tormentil 2.0 mg/kg	Iceland moss 10.0 mg/kg
Willow bark 2.0 mg/kg	

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## Heavy Metals: Food and Food Supplements

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- **Regulation (EC) No 1881/2006** setting maximum levels for certain contaminants in foodstuffs (in force since 1 March 2007, several amendments), e.g.
- Pb in vegetables excl. fresh herbs: 0.10 mg/kg  
Pb in berries and small fruit: 0.20 mg/kg
- Cd in vegetables excl. fresh herbs: 0.050 mg/kg  
Cd in fresh herbs: 0.20 mg/kg

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## Heavy Metals: Food and Food Supplements

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### Regulation (EC) No 1881/2006

- Pb in food supplements: 3.0 mg/kg
- Cd in food supplements: 1.0 mg/kg (except seaweed 3.0 mg/kg)



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## Heavy Metals: USP

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### **Draft monograph no. 2232: Elemental contaminants in dietary supplements**

- Individual component limits for arsenic 1.5 µg/g, cadmium 0.5 µg/g, lead 1.0 µg/g, mercury (total) 1.5 µg/g, methylmercury 0.2 µg/g
- 10 fold permitted daily exposure (PDE)
- Three options for compliance: (1) analysis of the serving size compared to PDE, (2) individual component option with daily intake of ≤ 10 g, (3) summation option for > 10 g daily intake or individual component limit exceeded

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## Heavy Metals: ICH

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### **Development of a Guideline Q3D on Metal Impurities**

- Proposal for class 1 metals („big four“): arsenic 1.5 ppm, cadmium 0.5 ppm, lead 1 ppm, mercury 1.5 ppm
- Class 2 metals (moderate safety concerns) and class 3 metals (low safety concern)
- „Herbals are excluded from the scope“

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## Microorganisms

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### Acceptance Criteria Ph.Eur.

- Chapter 5.1.4. Microbiological quality of non-sterile pharmaceutical preparations
- Chapter 5.1.8. Microbiological quality of herbal medicinal products for oral use:  
Categories A, B, C depending on treatment or pre-treatment which reduces microbial load

## Microorganisms

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### Acceptance Criteria Ph.Eur. 5.1.8, categories:

**A. Herbal medicinal products containing herbal drugs, with or without excipients, intended for the preparation of infusions and decoctions using boiling water (for example herbal teas, with or without added flavourings)**

TAMC (2.6.12)

Acceptance criterion:  $10^7$  CFU/g

Maximum acceptable count: 50 000 000 CFU/g

TYMC (2.6.12)

Acceptance criterion:  $10^5$  CFU/g

Maximum acceptable count: 500 000 CFU/g

*Escherichia coli* (2.6.31)

Acceptance criterion:  $10^3$  CFU/g

*Salmonella* (2.6.31)

Absence (25 g)

## Microorganisms

**B. Herbal medicinal products containing, for example, extracts and/or herbal drugs, with or without excipients, where the method of processing (for example, extraction) or, where appropriate, in the case of herbal drugs, of pre-treatment reduces the levels of organisms to below those stated for this category**

TAMC (2.6.12)

Acceptance criterion:  $10^4$  CFU/g or CFU/mL

Maximum acceptable count: 50 000 CFU/g or CFU/mL

TYMC (2.6.12)

Acceptance criterion:  $10^2$  CFU/g or CFU/mL

Maximum acceptable count: 500 CFU/g or CFU/mL

Bile-tolerant gram-negative bacteria (2.6.31)

Acceptance criterion:  $10^2$  CFU/g or CFU/mL

*Escherichia coli* (2.6.31)

Absence (1 g or 1 mL)

*Salmonella* (2.6.31)

Absence (25 g or 25 mL)

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## Microorganisms

**C. Herbal medicinal products containing, for example, extracts and/or herbal drugs, with or without excipients, where it can be demonstrated that the method of processing (for example, extraction with low strength ethanol or water that is not boiling or low temperature concentration) or, in the case of herbal drugs, of pre-treatment, would not reduce the level of organisms sufficiently to reach the criteria required under B**

TAMC (2.6.12)

Acceptance criterion:  $10^5$  CFU/g or CFU/mL

Maximum acceptable count: 500 000 CFU/g or CFU/mL

TYMC (2.6.12)

Acceptance criterion:  $10^4$  CFU/g or CFU/mL

Maximum acceptable count: 50 000 CFU/g or CFU/mL

Bile-tolerant gram-negative bacteria (2.6.31)

Acceptance criterion:  $10^4$  CFU/g or CFU/mL

*Escherichia coli* (2.6.31)

Absence (1 g or 1 mL)

*Salmonella* (2.6.31)

Absence (25 g or 25 mL)



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## Microorganisms

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### Method of Determination Ph.Eur.

- 2.6.12 and 2.6.13: Microbiological examination of non-sterile products
- 2.6.31: Microbiological examination of **herbal medicinal products** for oral use: TAMC and TYMC according to 2.6.12 plus tests on specified microorganisms

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## Mycotoxins (Medicinal Products)

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### German „Aflatoxin-Verbotsverordnung“

- Not more than 5 µg aflatoxin B<sub>1</sub> per kg and not more than 20 µg aflatoxins B<sub>1</sub>, B<sub>2</sub>, G<sub>1</sub> and G<sub>2</sub> per kg



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## Mycotoxins (Medicinal Products)

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### European Pharmacopoeia

- „Herbal Drugs“ and „Herbal Drugs for Homoeopathic Preparations“: „where appropriate, limits for aflatoxins/ a limit for ochratoxin A ... may be required“



- Liquorice dry extract and Liquorice dry extract for flavouring purposes: 80 µg/kg ochratoxin A

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## Mycotoxins (Food)

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- **Regulation (EC) No 1881/2006** setting maximum levels for certain contaminants in foodstuffs

- Aflatoxins in nuts: B<sub>1</sub> 2.0-8.0, sum 4.0-15.0 µg/kg

- Aflatoxins in spices\*: B<sub>1</sub> 5.0, sum 10.0 µg/kg

\* Capsicum spp., Piper spp., nutmeg, ginger, turmeric



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## Mycotoxins (Food)

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### Regulation (EC) No 1881/2006

- Ochratoxin A in dietary foods for special medical purposes intended for children: 0.50 µg/kg
- Ochratoxin A in spices\*: 30 µg/kg from 1 July 2010 and 15 µg/kg from 1 July 2012
- Ochratoxin A in liquorice root: 20 µg/kg
- Ochratoxin A in liquorice extract: 80 µg/kg

\* Capsicum spp., Piper spp., nutmeg, ginger, turmeric

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## Mycotoxins (USP)

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### USP Chapter 561: Articles of Botanical Origin

- Not more than 5 µg aflatoxin B<sub>1</sub> per kg and not more than 20 µg aflatoxins B<sub>1</sub>, B<sub>2</sub>, G<sub>1</sub> and G<sub>2</sub> per kg
- The extend of testing may be determined using a risk-based approach that considers the likelihood of contamination, and the presence of unexpected contamination is to be considered in determining compliance

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## Polycyclic Aromatic Hydrocarbons

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### Regulation 835/2011 amending 1881/2006

- Benzo(a)pyrene in **oils and fats** (excluding cocoa butter) intended for direct human consumption or use as an ingredient in foods: 2.0 µg/kg
- From 1 September 2012: sum of benzo(a)pyrene, benzo(a)anthracen, chrysene and benzo(b)fluoroanthene: 10.0 µg/kg

## Plant Protection Products: Limits

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- European Pharmacopoeia Chapter 2.8.13
- Regulation No 396/2005 on **maximum residue levels of pesticides** in or on food and feed of plant and animal origin



## Plant Protection Products: Limits

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### European Pharmacopoeia (Ph.Eur.) 2.8.13

- List of 70 substances plus metabolites and respective limits
- Further substances: reference to Regulation 396/2005 oder calculation of limit
- Validated method to be used
- Activities of the BAH Working Group on Contaminants: database containing numerous findings from daily practice of the companies

## Plant Protection Products: Limits

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### Regulation No 396/2005:

### Website of the European Commission

- Amendments:  
[http://ec.europa.eu/food/plant/protection/pesticides/community\\_legislation\\_en.htm](http://ec.europa.eu/food/plant/protection/pesticides/community_legislation_en.htm)
- Database (by products and by substances):  
[http://ec.europa.eu/sanco\\_pesticides/public/index.cfm](http://ec.europa.eu/sanco_pesticides/public/index.cfm)

## Plant Protection Products: Limits

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### Annexes to Regulation 396/2005

- I: (Groups of) products to which MRLs apply (including herbal teas)
- II: MRLs formerly defined for products under EC Directives
- III: Temporary MRLs for defined products
- IV: Substances for which no MRLs are required
- (V and VI not yet published, e.g. conversion factors for processed commodities)
- VII: Fumigants

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## Plant Protection Products: Authorisation

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- **Regulation (EC) No 1107/2009** concerning the placing of plant protection products on the market (in force since 14 June 2011)
- Harmonised rules for the approval of active substances and placing on the market of plant protection products including mutual recognition (climatic zones with comparable conditions)
- Approval of active substances plus authorisation of plant protection products

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## Plant Protection Products : Authorisation

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### Regulation (EC) No 1107/2009

- The authorisation of a plant protection product may be extended to **minor uses** (Article 51)
- Defined as use on plants or plant products which are not widely grown („Lückenindikationen“)
- E.g. uses against specific pests/ diseases on medicinal plants

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## Integrated Pest Management

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- **Directive 2009/128/EC** establishing a framework for Community action to achieve the sustainable use of pesticides
- “Member States shall adopt **National Action Plans** to set up their quantitative objectives, targets, measures and timetables to **reduce risks and impacts of pesticide use** on human health and the environment and to encourage the development and **introduction of integrated pest management** and of alternative approaches or techniques in order to reduce dependency on the use of pesticides.”

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## Integrated Pest Management

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- “... keep the use of plant protection products and other forms of intervention to **levels that are economically and ecologically justified** and **reduce or minimise risks to human health and the environment.**”
- “Member States shall establish appropriate incentives to encourage professional users to implement **crop or sector-specific guidelines** for integrated pest management on a voluntary basis. Public authorities and/or organisations representing particular professional users may draw up such guidelines ...”

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## Integrated Pest Management

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### Annex III: General principles of integrated pest management

- Prevention/suppression of harmful organisms, e.g. crop rotation, cultivation, seed and planting material, fertilisation, irrigation, hygiene, beneficial organisms
- Monitoring by adequate methods
- Decision on whether to apply plant protection measures
- Preference of sustainable non-chemical measures
- Application of pesticides
- Level/extent of use
- Risk of resistance
- Recording and checking success



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## Integrated Pest Management

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- Joint project of the German Committee on Medicinal and Spice Plant Cultivation (DFA) and the German Medicines Manufacturers' Research Association (FAH):
- Development of **sector-specific guidelines for medicinal and spice plants** in accordance with Article 14 and Annex III of CD 2009/128/EC
- Detailed guidance on how to implement the general criteria to this sector
- Crop-specific guidance might follow

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## Summary and Conclusion

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- High quality requirements, in particular on contaminants, for herbal medicinal products and related areas guarantee optimum consumer protection
- Realistic criteria as well as practical experiences should be taken into consideration when new rules are established and when limits are set
- Preventive measures e.g. reduction of the use of pesticides where justified would minimise the risks to human health and to the environment

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