
Taking the risk of the benefit
Gert Laekeman
The unbalanced situation of herbal medicines

OBJECTIVES

- Context
- Methodological approach
- Examples
- Facilitating vs hampering marketing authorisation

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16/07/2010 **Committee for Medicinal Products for Veterinary Use (CVMP) Meeting of 13-15 July 2010**

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15/07/2010 **European Medicines Agency launches new website**

The European Medicines Agency today unveiled its new corporate website at www.ema.europa.eu. The site has been completely redesigned and rebuilt to optimize usability for the Agency's key online audiences and build on existing activities to improve

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What we do

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The European Medicines Agency (EMA) is a decentralised body of the European Union, located in London. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

- The Agency is responsible for the scientific evaluation of applications for European marketing authorisations for both human and veterinary medicines (centralised procedure). Under the centralised procedure, companies submit a single marketing-authorisation application to the Agency. Once granted by the European Commission, a centralised (or 'Community') marketing authorisation is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway).

- All medicines for human and animal use derived from biotechnology and other high-tech processes must be approved via the centralised procedure. The same applies to all advanced-therapy medicines and human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases. Similarly, all veterinary medicines intended for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals have to go through the centralised procedure.

- For medicines that do not fall under any of the above-mentioned categories

Related information

- Agency Structure

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Committees

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Scientific evaluation on applications from pharmaceutical companies is carried out by six Scientific Committees. These Committees normally meet on a monthly basis and are comprised of members nominated by the Member States. Assessments are based on purely scientific criteria and determine whether or not the medicines concerned meet the necessary quality, safety and efficacy requirements (in accordance with EU legislation, particularly Directive 2001/83/EC). These processes ensure that medicines have a positive risk-benefit balance in favour of patients/users of these products once they reach the marketplace.

- Committee for Medicinal Products for Human Use (CHMP)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Paediatric Committee (PDCO)
- Committee for Advanced Therapies (CAT)

Committee on Herbal Medicinal Products (HMPC)

The Committee on Herbal Medicinal Products (HMPC) was established in September 2004, replacing the CPMP Working Party on Herbal Medicinal Products. The Committee was established in accordance with Regulation (EC) No 726/2004 and Directive 2004/24/EC, which introduced a simplified registration procedure for traditional herbal medicinal products in EU Member States.

▸ Full overview of the role of the HMPC

Composition

The HMPC is composed of scientific experts in the field of herbal medicinal products. It has one member and one alternate member nominated by each of the 27 EU Member States and by each of the EEA-EFTA states Iceland and Norway. The Chair is elected by serving HMPC members.

Up to five additional members (European experts nominated by the Member States or by the Agency) may be co-opted to contribute additional expertise to the HMPC. Currently, the Committee has co-opted members with expertise in clinical pharmacology, experimental/non-clinical pharmacology, toxicology, paediatric medicine and general and family medicine.

The HMPC also has observers from the European Directorate for the Quality of Medicines (EDQM) and - as part of the EU Enlargement Programme 'Transition Instrument for Pre-accession programme' - from Croatia, the Former Yugoslav Republic of Macedonia, Montenegro, Serbia and Turkey.

See HMPC members for the list of current members.

Meeting calendar

See full meeting planning for 2010

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hypericum

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Hypericum

Key documents

Name	Language	First published	Last updated
Final community herbal monograph on Hypericum perforatum L., herba (well-established medicinal use)	(English only)	20/12/2009	
Final community herbal monograph on Hypericum perforatum L., herba (traditional use)	(English only)	20/12/2009	
Opinion of the Committee on Herbal			

Additional information

- Read more about the Agency's role in herbal medicinal products
- Read more about Community Monographs
- Read more about Community list entries
- Read more about submission of data
- Read more about Public Consultations
- Read more about the Committee on Herbal Medicinal Products (HMPC)

E/S/C/O/P Monographs

The Scientific Foundation for Herbal Medicinal Products

Second edition

Supplement 2009

E/S/C/O/P
European Scientific Cooperative On Phytotherapy

Thieme

EFSA Topic: Nutrition and Health Claims - Windows Internet Explorer

http://www.efsa.europa.eu/en/ndatopics/topic/nutrition.htm

EFSA Topic: Nutrition and Health Claims

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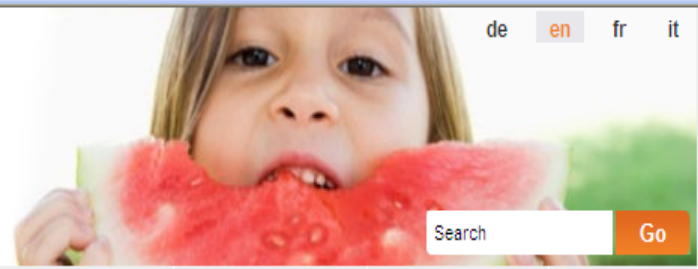
efsa

European Food Safety Authority

Committed to ensuring that Europe's food is safe



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Nutrition and Health Claims

An in
claim
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EU framework

EU decision makers adopted a Regul
December 2006. This Regulation lays
nutritional claims on foodstuffs based

One of the key objectives of this Regulation is to ensu made on a food label in the EU is clear and substantiated by scientific evidence. EFSA is responsible for verifying the scientific substantiation of the submitted claims, some of which are currently in use, some of which are proposed by applicants. This information serves as a basis for the European Commission and Member States, which will decide whether to authorise the claims.

EFSA's tasks

EFSA's work includes providing scientific advice on:

... EFSA is responsible for verifying the scientific substantiation of the submitted claims, some of which are currently in use, some of which are proposed by applicants ...

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Herbals

Herbal preparations

Food supplement

- notification
- 'claim'
- information to public
- HACCP

EFSA

Herbal medicine

- registration
- therapeutic indication
- SmPC / PPI
- GMP

EMA - HMPC

Food supplement	Traditional Herbal Medicine
People	
General population ?	In- / exclusion Population at risk
Process	
Preparation ?	Well-defined preparations
Duration of use ?	Limited duration of use
Product	
Outcome: cf claim ?	Outcome: cf. indication

OBJECTIVES

- Context
- **Methodological approach**
- Examples
- Facilitating vs hampering marketing authorisation

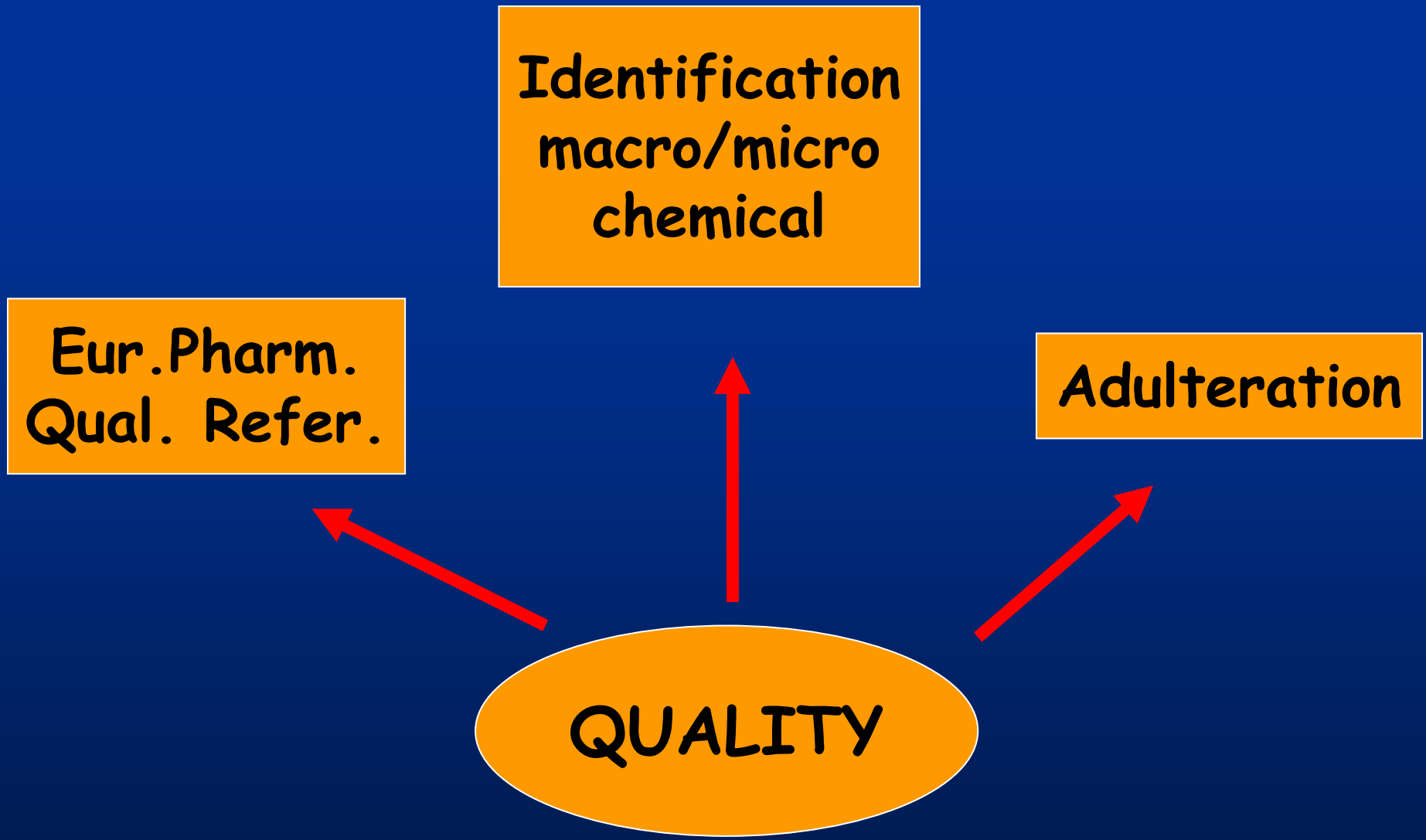
HERBAL MEDICINES

- Quality
- Safety
- Effectiveness

BENEFIT  RISK

25 questions

No risk	**Therapeutic benefit**
No therapeutic benefit	Risk


Identification
macro/micro
chemical
Eur.Pharm.
Qual. Refer.
Adulteration
QUALITY

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  - European Pharmacopoeia 6.8
  - Pharmacopée Européenne 6.8

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... The material complies with the European Pharmacopoeia monograph ...

This application requires Acrobat Reader. We recommend using version 8 or higher. Download a copy here.

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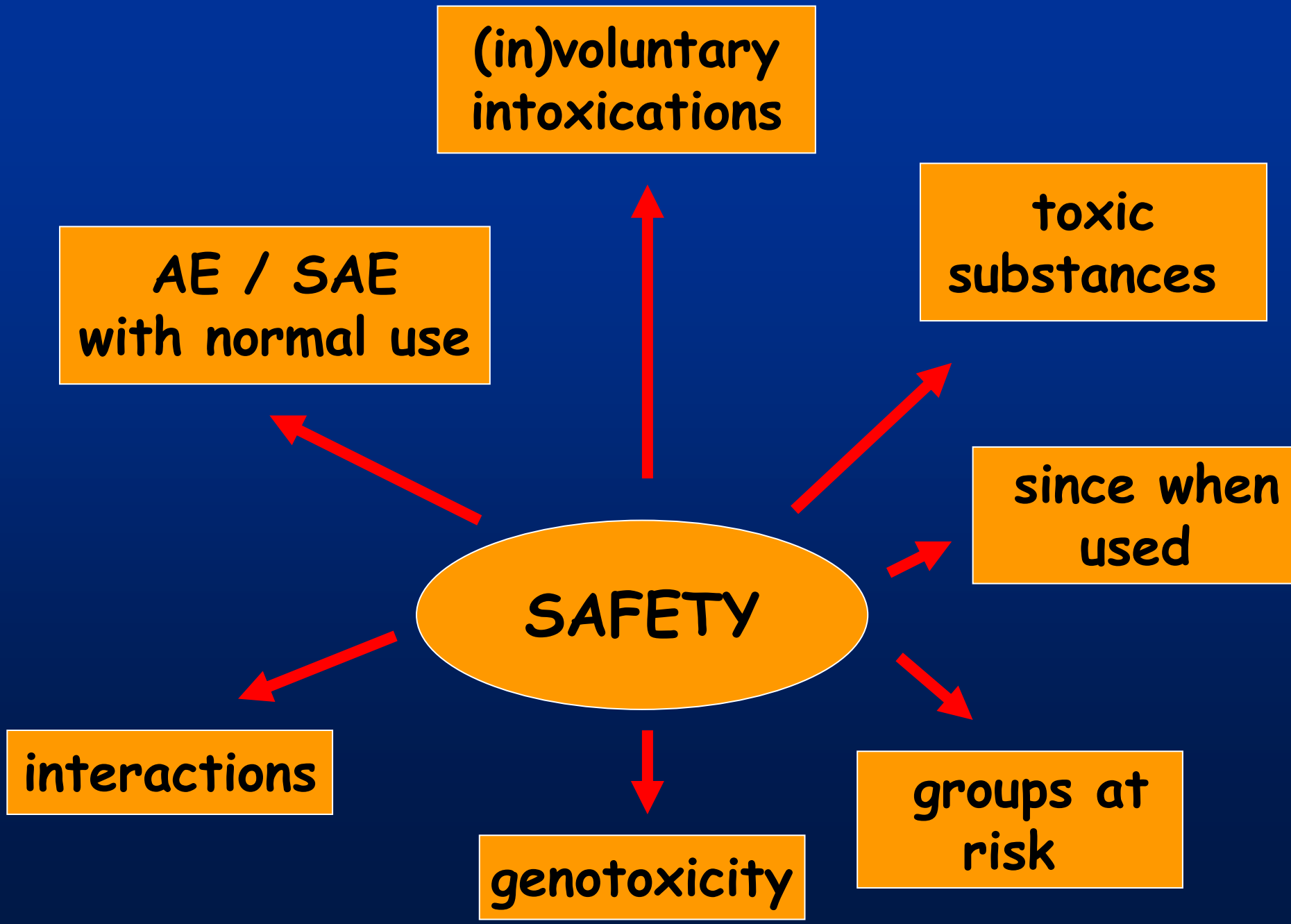
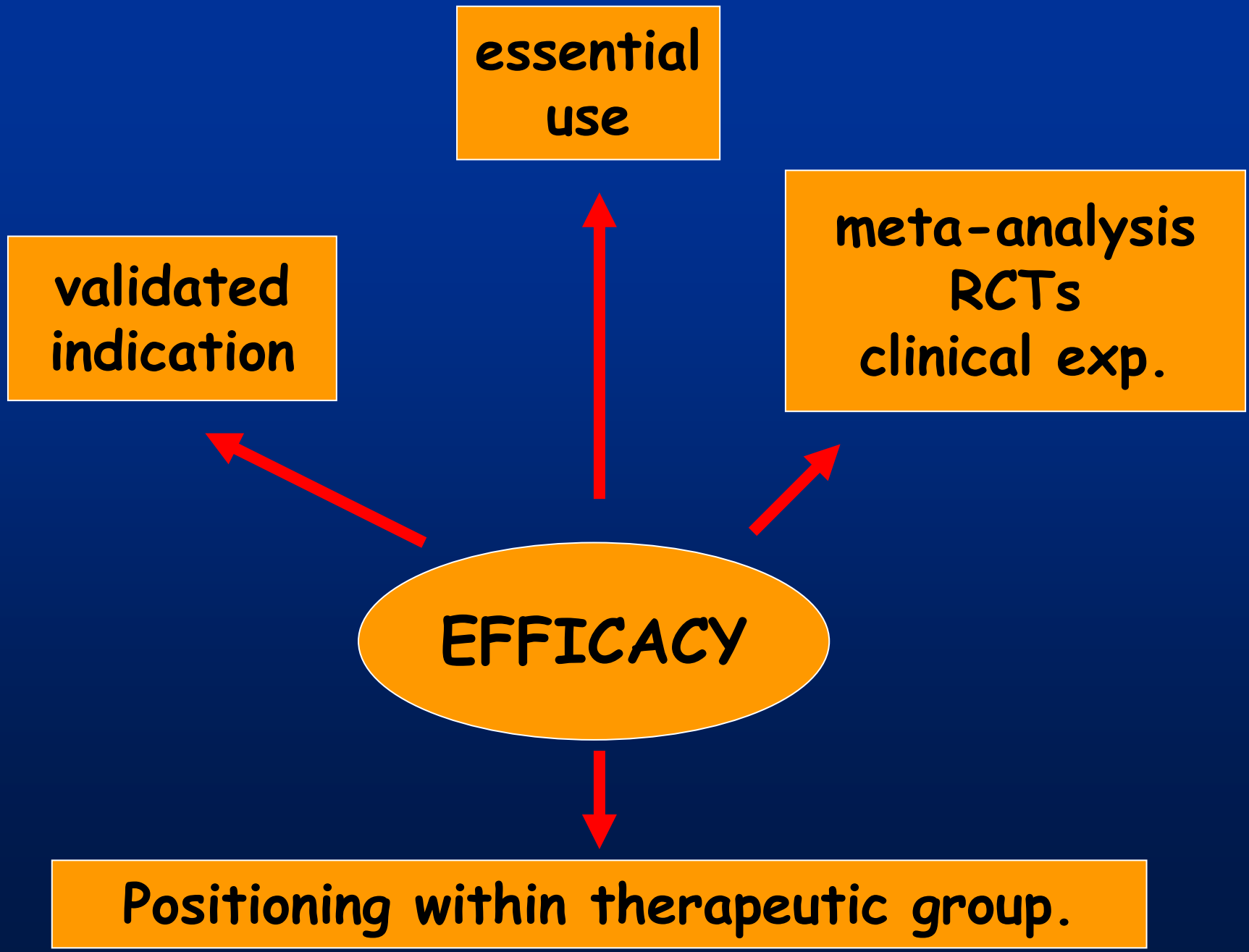

(in)voluntary intoxications
toxic substances
AE / SAE with normal use
since when used
SAFETY
interactions
groups at risk
genotoxicity

Pharmaceutical Press

Stockley's
Herbal Medicines Interactions

Edited by **Elizabeth Williamson, Samuel Driver and Karen Baxter**


essential use
validated indication
meta-analysis RCTs clinical exp.
EFFICACY
Positioning within therapeutic group.

OBJECTIVES

- Context
- Methodological approach
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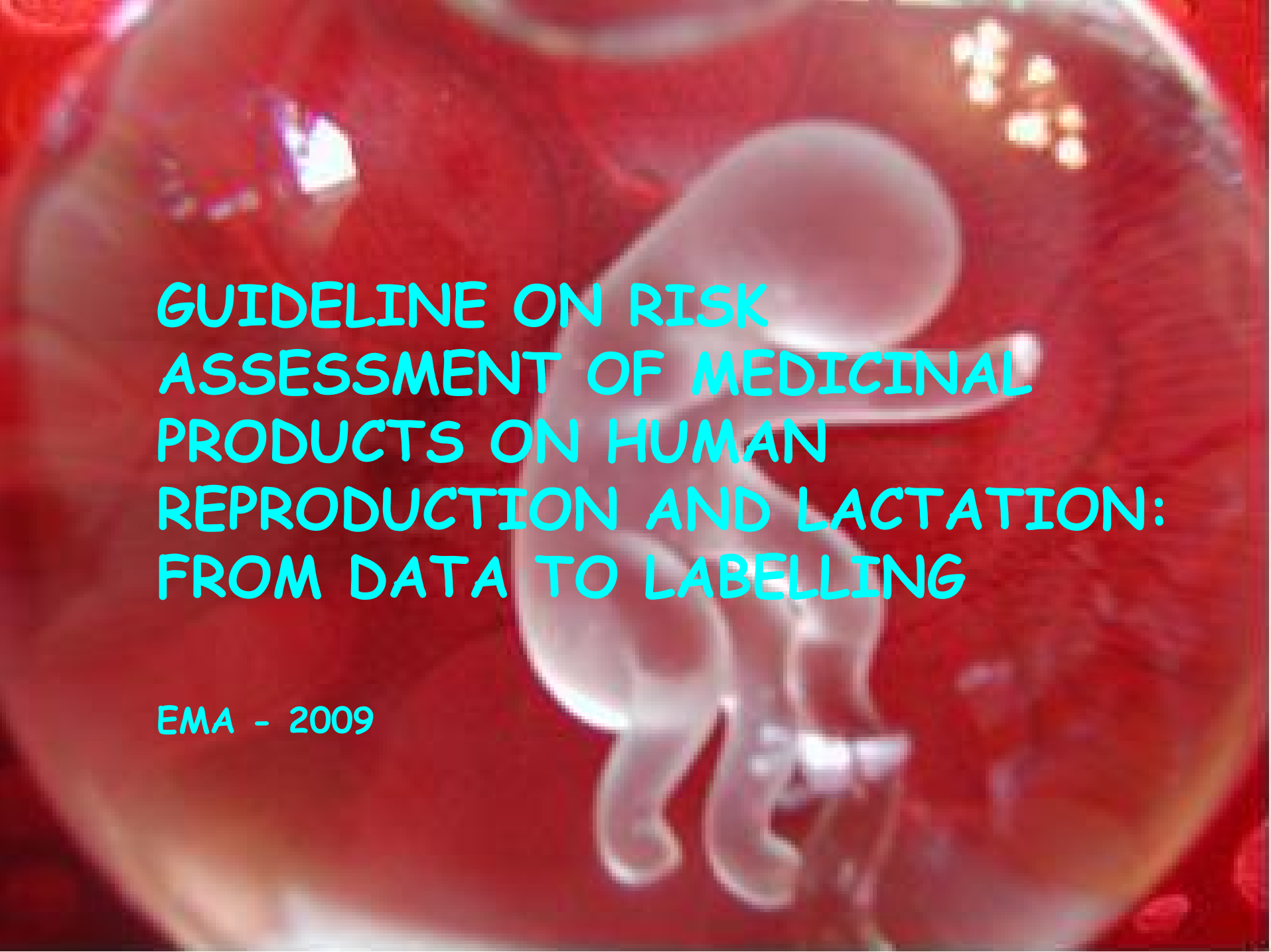
HERBALS USE

- People: patients / consumers
- Process: intervention / event
- Product: (therapeutic) outcome



GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING

EMA - 2009

… can be used during pregnancy.

No effects during pregnancy are anticipated, since systemic exposure to {Active substance} is negligible

e.g. Avenae sativae fructus

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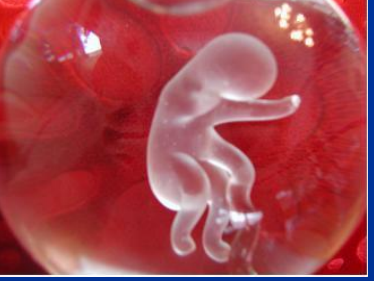

… can be used ‹during pregnancy › ‹during {… trimester} of pregnancy › if clinically needed …

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity

- Systematic pharmacovigilance of occasional exposure: only possible in pharmaceutical/medical environment
- Specific for herbal medicinal product !

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REPORTING ADVERSE EVENTS

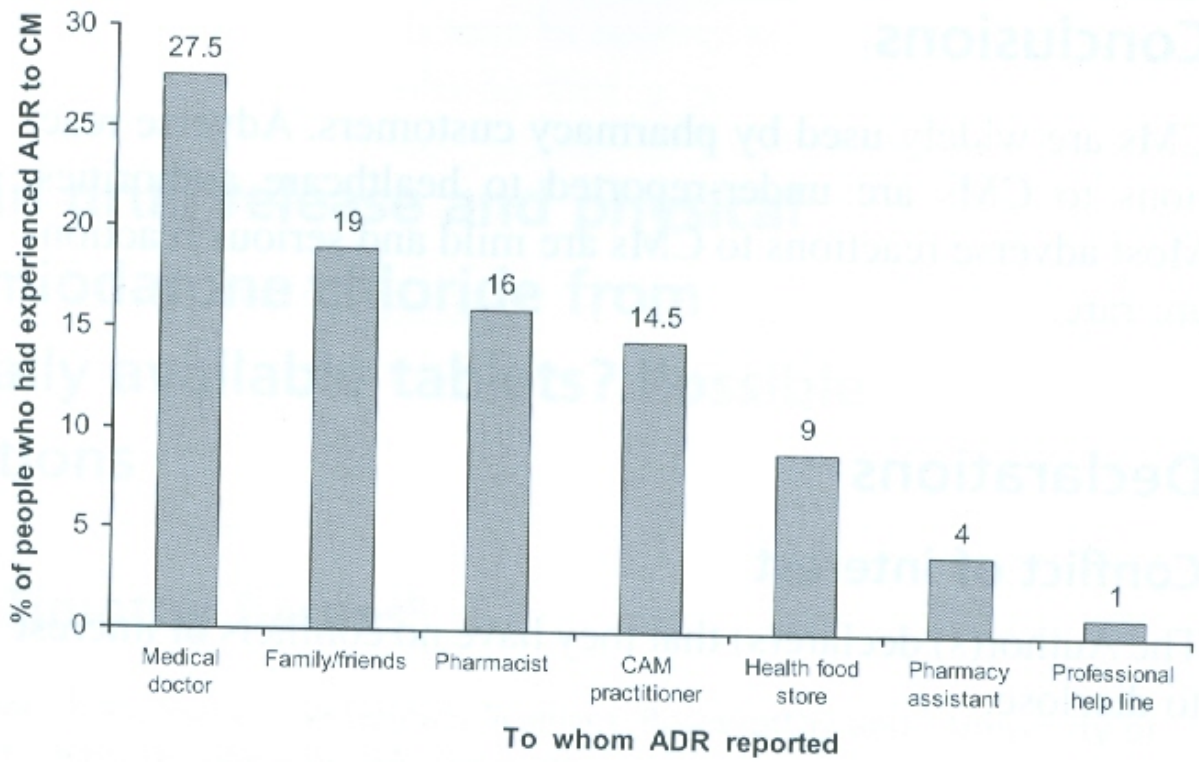

Figure 1 Responses from consumers of complementary medicine who had experienced an adverse reaction to the question 'Who did you tell about the adverse reaction?' ADR, adverse drug reaction; CAM, complementary and alternative medicine; CM, complementary medicine.

Braun et al. Adverse reactions to complementary medicines: the Australian pharmacy experience. Int. J. Pharm. Practice 2010; 18: 242-244.

… The use of … may be considered ‹during pregnancy › ‹during {… trimester} of pregnancy ›, if necessary …

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity›. Animal studies do not indicate reproductive toxicity

Within reach for TU herbal products

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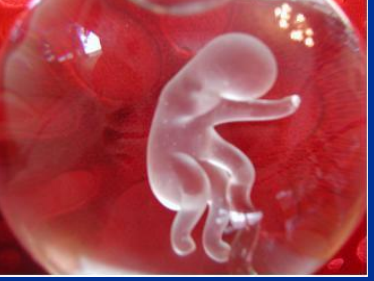

… As a precautionary measure, it is preferable to avoid the use of … ‹during pregnancy › ‹during {… trimester} of pregnancy › …

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use in pregnant women›
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity

Most of the herbal medicinal products

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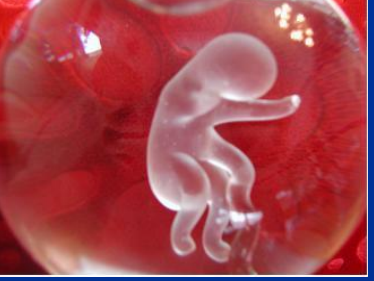

… is not recommended ‹ during pregnancy › ‹during {… trimester} of pregnancy › and in women of childbearing potential not using contraception …

There are no or limited amount of data from the use of {Active substance} in pregnant women›
A. Studies in animals have shown reproductive toxicity
or
B. Animal studies are insufficient with respect to reproductive toxicity

e.g. essential oils or reports on isolated compounds

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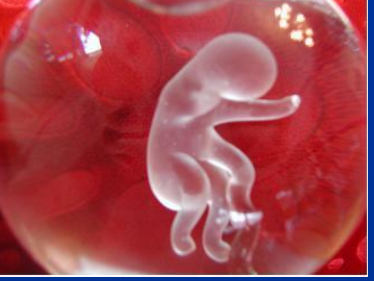

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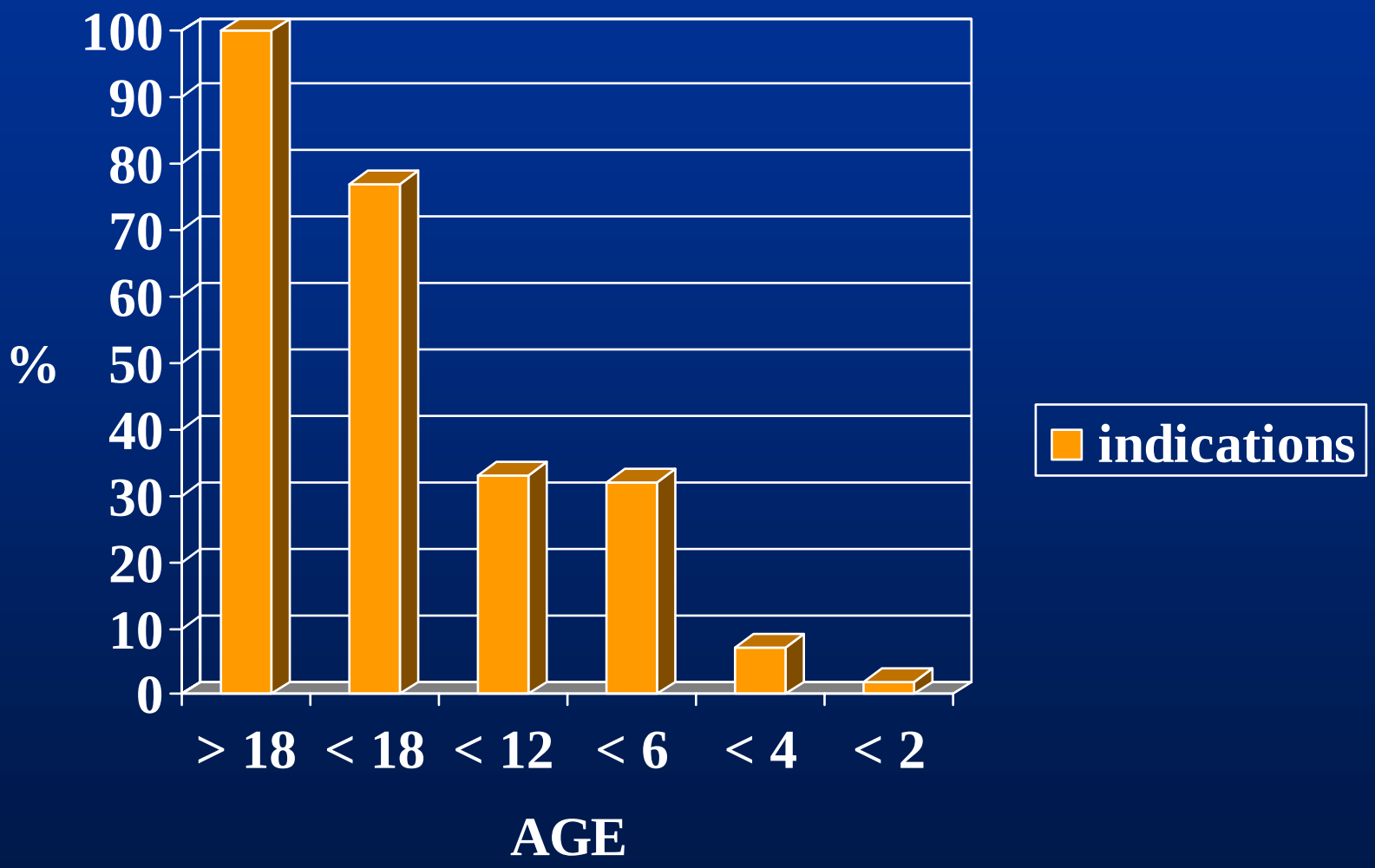
RESTRICTIONS TRADITIONAL USE



HERBALS USE

- People: patients / consumers
- Process: intervention / event
- Product: (therapeutic) outcome

2001-83-EC

Specific provisions applicable to traditional herbal medicinal products

… Bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community …

Marketed herbal medicine?

Formulary ?

Camellia sinensis

… Fulminant hepatitis during self-medication with hydroalcoholic extract of green tea …

Exolise = 80% ethanolic extract of Camellia sinensis

- On the market in B, E, F & UK > 1999
- 25% catechins

Gloro et al. Eur J Gastroenterol Hepatol. 2005; 17 (10): 1135-7.

WARNINGS & RESTRICTIONS

Belgium: RC 1997 & 2005

Population based

- Ginkgo biloba: anticoagulants !
- Hypericum perforatum (St.Johnswort); other medicines !
- Glycyrrhiza glabra (licorice): limit of 6 weeks !
- Rheum (rubarb) & Senna: ≥ 12y / medical advice / pregnancy
- Urtica (common nettle): advice doctor / pharmacist

Posology based

Daily dose restricted to ≤ 80% of minimal therapeutic dose

HERBALS USE

- People: patients / consumers
- Process: intervention / event
- Product: (therapeutic) outcome

Toxicity of *Passiflora incarnata* L.

Alex A. Fisher; Patrick Purcell; David G. Le Couteur

The Canberra Hospital, Garran, Australia (AAF); Therapeutic Goods Administration, Symonston, Australia (PP); The Canberra Clinical School of the University of Sydney, Garran, Australia (AAF; DGLC)

ABSTRACT

Background: Herbal medicines may have significant adverse effects which are not suspected or recognized. Case Report: A 34-year-old female developed severe nausea, vomiting, drowsiness, prolonged QT_c, and episodes of nonsustained ventricular tachycardia following self-administration of a herbal remedy, *Passiflora incarnata* L., at therapeutic doses. The possible association of symptoms with passiflora was not recognized for several days. She required hospital admission for cardiac monitoring and intravenous fluid therapy. Conclusions: *Passiflora incarnata* was associated with significant adverse effects in this patient. It is important to ask specifically about the use of herbal medicines in patients with undiagnosed illnesses.

CAUSAL RELATIONSHIP

Austin Bradford-Hill criteria

(Environment & disease)

- Strenght
- Consistency
- Temporality
- Biological gradient
- Specificity
- Coherence
- Experimental evidence
- Analogy

[Shakir & Layton, Drug Safety 2002; 25: 467-471]

CAUSAL RELATIONSHIP

Strength of associations

e.g. smoking – lung cancer (10-30)
= strong association

Fisher et al. 2000

Causality based on strength = absent

CAUSAL RELATIONSHIP

Consistency of findings

- Different populations
- Different circumstances

Fisher et al. 2000

One case in 34-year old Caucasian female
- Other females in other countries ?
- Male patients
- Different age ?

CAUSAL RELATIONSHIP

Specificity of associations

= linked to preparation

- what is known about the preparation ?

Fisher et al. 2000

... Sedacalm contains 500 mg of the active ingredients ...

Characterisation: digitalis glycosides excluded by analysis, but methodology not specified

CAUSAL RELATIONSHIP

Temporality

- first cause
- than effect !

Fisher et al. 2000

QTc occurred after taking the herbal but also after taking metoclopramide, prochlorperazine, droperidol & ondansetron

CAUSAL RELATIONSHIP

Biological gradient

- dose dependency of ADR
- duration of therapy

Fisher et al. 2000

No dose-relationship dressed
Short duration of therapy

CAUSAL RELATIONSHIP

Coherence

= … the cause-and-effect interpretation whose data should not seriously conflict with generally known facts of the natural history and biology of a disease …

Fisher et al. 2000

No coherence: publication about a cardioprotective action in pigs

[Peeters E, et al. Effect of supplemental tryptophan, vitamin E and a herbal product on responses by pigs to vibration. J. Anim. Sci. 2004; 82 (8): 2410-2120]

CAUSAL RELATIONSHIP

Experimental evidence

= observations to be completed by experimental evidence in biological models

Fisher et al. 2000

No such evidende from *in vitro* or *in vivo* models reported in literature

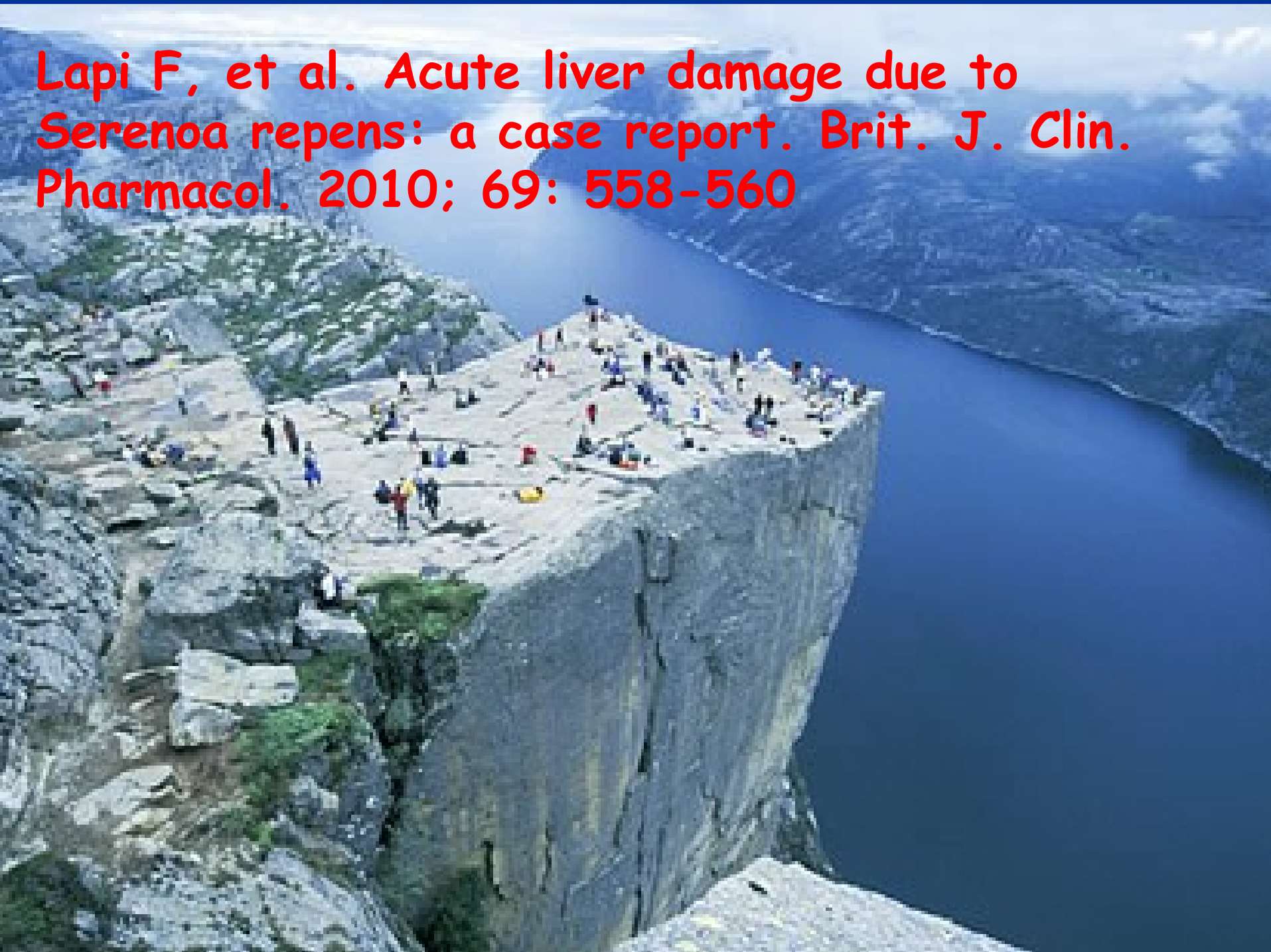
CAUSAL RELATIONSHIP

Analogy

= mostly based on 'class' effects

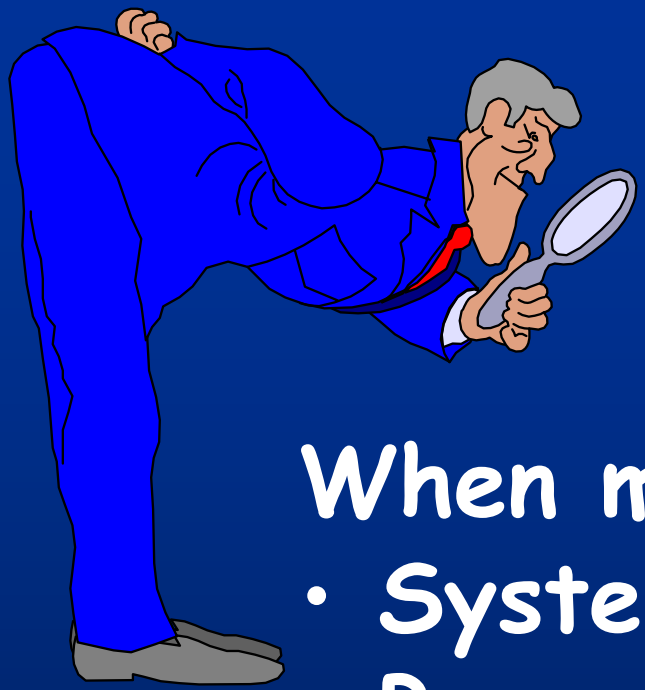
Fisher et al. 2000

Passiflora does not belong to a defined class
Properties of secondary metabolites known and not including the described risk


Lapi F, et al. Acute liver damage due to Serenoa repens: a case report. Brit. J. Clin. Pharmacol. 2010; 69: 558-560

58y male Caucasian

- Exclusion of co-medication
- Liver enzymes quantified
- Virus markers detected: only CMV IgG positive but no antigen in blood sample
- Follow-up of patient with check after 1 year
- Fatty acids in capsules quantified (chromatogram included) and heavy metals excluded
- References on other case reports included



HERBALS
BENEFIT / RISK

When making an approach

- System for evaluation
- Pro-active pharmacovigilance
- Protection of licences
- Critical causality analysis