Bundesinstitut
für Arzneimittel
und Medizinprodukte

Bewertung des kanzerogenen Risikos von Estragol

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Disclaimer

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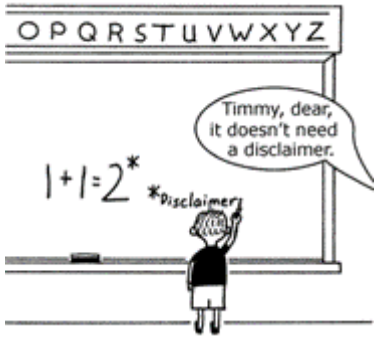
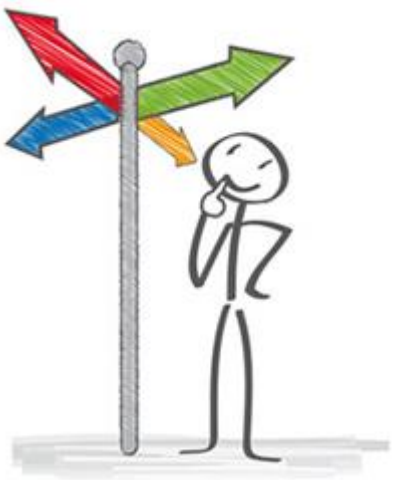


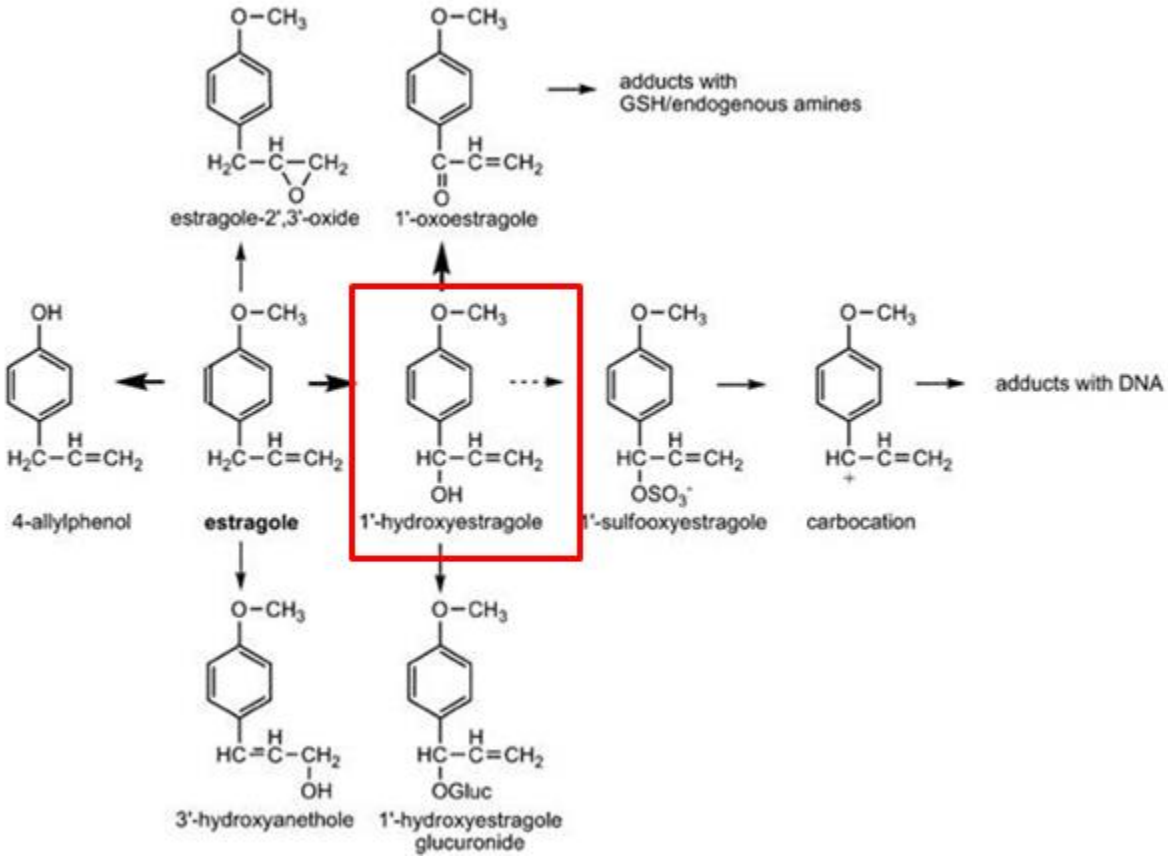
Schwerpunkte

- Estragol / Bewertung der Unterlagen zu Estragol
- Besonderheiten von (pflanzlicher) Arzneimittel und ihre rechtliche Einordnung
- EMA/EFSA
- „Established rules of scientific assessment“ of risks?
- Ansätze zur Berechnung von Grenzwerten („Faktoritis“?)
- Was fehlt?



Estragol

Phenylpropanoid (Eugenol, Isoeugenol, Methyleugenol, Safrol, Isosafrol, Anethol, Elemicin, Myristicin, Apiol)



Estragol

Table 1: Main occurrence of estragole in plants and/or essential oils (modified from EFSA, 2009, based principally on Council of Europe publications)

Botanical name	Common name	Essential oil in plant (%)/estragole in essential oil (%)	Estragole in part of plant used (%)
Agastache foeniculum (Pursh.) Ktze. (syn. *Lophantus anisatus A. anethiodora, A. anisata*) (Lamiaceae)	Anise hyssop, Giant hyssop, Liquorice mint	? / 74	
Anthriscus cerefolium (L.) Hoffm. ssp *cerefolium* (Apiaceae)	(Garden) chervil	0.9 in fruit/up to 85	max. 0.8
Artemisia dracunculus L. (Asteraceae)	Tarragon	0.25-1 in herb/60-75	0.7
Foeniculum vulgare Mill. subsp. vulgare var. *vulgare* (syn. *Foeniculum vulgare* Mill. var. dulce (Mill.) Batt. et Trab.) (Apiaceae)	Sweet fennel, Roman fennel	? / 1.5-5.0	
Foeniculum vulgare Mill. subsp. vulgare var. vulgare (syn. *Foeniculum vulgare* var. vulgare) (Apiaceae)	Bitter fennel, Common fennel	2-6 in fruit/3.5-12.0	0.3
Illicium verum Hook f. (Magnoliaceae)	Star-anise	5 in fruit/5-6l	max. 0.25
Melissa officinalis L. (Lamiaceae)	Lemon balm	no info/6.3	
Myrrhis odorata (L.) Scop (Apiaceae)	Sweet chervil	no info/up to 75	
Ocimum basilicum L. (Lamiaceae)	Sweet basil	0.8 in herb/20-89	approx. 0.4
Pimpinella anisum L. (Apiaceae)	Anise, Sweet cumin	1-4 in fruit/1-5	max. 0.2

Estragol

Table 9: Overview of the data from Miller et al. (1983) on the incidence of hepatomas in female mice exposed for 12 months via the diet to estragole

dose	Estimated dose mg/kg bw/day	No of animals	No of mice with hepatomas	incidence
0	0	43	0	0
0.23% in diet	150-300	48	27	56
0.46% in diet	300-600	49	35	71

*ESCO Report "Advice on the EFSA guidance document for the safety assessment of botanicals and botanical preparations intended for use as food supplements, based on real case studies" (EFSA Journal 2009; 7(9):280)

in EFSA (2009)*: $BMDL_{10}$ = zwischen 9 und 33 mg/kg/Tag (weibl. Mäuse)

Estragol

= genotoxisches Karzinogen

SCF (Scientific Committee on Food) 2001:
Opinion of the Scientific Committee on Food on Estragole (1-allyl-4-methoxybenzene). SCF/CS/FLAV/FLAVOUR/6 ADD 2 Final, 26.09.2001.

CoE (Council of Europe) 2005:
Estragole. in: Active principles (constituents of toxicological concern) contained in natural sources of flavouring. 2005, 76-86

HMPC 2005:
Public statement on the use of herbal medicinal products containing Estragole (EMA/HMPC/137212/2005)

EFSA 2009:
ESCO Report "Advice on the EFSA guidance document for the safety assessment of botanicals and botanical preparations intended for use as food supplements, based on real case studies." EFSA Journal 2009; 7(9):280)

Estragol – NTP, 2011

- Gruppen von jeweils 10 männl. und 10 weibl. Ratten und Mäusen
- 5 Tage/Woche
- Dosierungen:
  0 mg/kg; 37.5 mg/kg; 75 mg/kg; 150 mg/kg; 300 mg/kg; 600 mg/kg

Under the conditions of these 3-month studies, estragole showed carcinogenic activity based on the occurrence of two cholangiocarcinomas and one hepatocellular adenoma in the liver of three of 10 male F344/N rats in the high dose group. Because rats and mice were exposed for only 3 months, these studies do not assess the full carcinogenic potential of estragole.

Nonneoplastic effects were observed in the liver, glandular stomach, nose, kidney, and salivary gland of male and female rats and in the testes, epididymides, and pituitary gland of male rats. Nonneoplastic effects were also observed in the liver and nose of male and female mice and in the stomach of female mice.

Estragol – NTP, 2011 (Ratten)

	Männliche Tiere	Weibliche Tiere
600 mg/kg	**2 animals = multiple cholangiocarcinomas** **1 animal = hepatocellular adenoma** all animals = cholangiofibrosis	incidences of eosinophilic focus increased
ab 300 mg/kg	incidences of eosinophilic focus increased	
ab 150 mg/kg	incidences of basophilic and mixed cell foci increased	all animals = hepatocellular hypertrophy incidences of basophilic and mixed cell foci increased incidences of cellular infiltration of the periportal region by histiocytes increased
ab 75 mg/kg	all animals = hepatocellular hypertrophy	
alle Dosisgruppen	incidencies of bile duct hyperplasia; oval cell hyperplasia, chronic periportal inflammation increased incidences of cellular infiltration of the periportal region by histiocytes increased	incidencies of bile duct hyperplasia; oval cell hyperplasia, chronic periportal inflammation increased

Estragol – NTP, 2011 (Mäuse)

	Männliche Tiere	Weibliche Tiere
600 mg/kg	**1 animal = death (liver necrosis) in week 9** all animals = cholangiofibrosis	**all animals = death (liver necosis) in week 1**
ab 300 mg/kg	incidences of hepatocellular hypertrophy and oval cell hyperplasia increased	
ab 150 mg/kg		incidences of hepatocellular hypertrophy increased
ab 75 mg/kg		incidences of oval cell hyperplasia increased

(Pflanzliche) Arzneimittel

Grundlage ist das Arzneimittelgesetz (AMG)

§2 Arzneimittelbegriff

(1) Arzneimittel sind Stoffe oder Zubereitungen aus Stoffen,

1. die zur Anwendung im oder am menschlichen oder tierischen Körper bestimmt sind und als Mittel mit Eigenschaften zur Heilung oder Linderung oder zur Verhütung menschlicher oder tierischer Krankheiten oder krankhafter Beschwerden bestimmt sind oder

2. die im oder am menschlichen oder tierischen Körper angewendet oder einem Menschen oder einem Tier verabreicht werden können, um entweder
   a) die physiologischen Funktionen durch eine pharmakologische, immunologische oder metabolische Wirkung wiederherzustellen, zu korrigieren oder zu beeinflussen oder
   b) eine medizinische Diagnose zu erstellen.

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Abgrenzung

Pflanzliche Arzneimittel

Arzneimittel: wirken pharmakologisch, immunologisch oder metabolisch

Kosmetische Mittel

kommen äußerlich mit Teilen des menschlichen Körpers oder der Mundhöhle in Berührung; sollen reinigen, parfümieren, schützen, in guten Zustand erhalten, Aussehen verändern oder Körpergeruch beeinflussen; können physiologische Wirkung haben – überwiegend sollte Wirkung aber kosmetischer Art sein

Medizinprodukte

bestimmungsgemäße Hauptwirkung nicht pharmakologisch, immunologisch oder metabolisch sondern

z.B. primär physikalisch

z.B. Implantate, Produkte zur Injektion, Infusion, Transfusion und Dialyse, Herzschrittmacher, Dentalprodukte, Verbandstoffe, Sehhilfen, Röntgengeräte, Kondome

Nahrungsergänzungsmittel

Lebensmittel, die allgemeine Ernährung ergänzen; haben ernährungsspezifische oder physiologische Wirkung

z.B. Vitamine, Spurenelemente, essentielle Fettsäuren, Aminosäuren

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(Pflanzliche) Arzneimittel

Grundlage ist das Arzneimittelgesetz (AMG)

§4 Sonstige Begriffsbestimmungen

(28) Das **Nutzen-Risiko-Verhältnis** umfasst eine Bewertung der positiven therapeutischen Wirkungen des Arzneimittels im Verhältnis zu dem Risiko nach Absatz 27 Buchstabe a, bei zur Anwendung bei Tieren bestimmten Arzneimitteln auch nach Absatz 27 Buchstabe b.

(27) Ein mit der Anwendung des Arzneimittels verbundenes Risiko ist
(a) jedes Risiko im Zusammenhang mit der Qualität, Sicherheit oder Wirksamkeit des Arzneimittels für die Gesundheit des Patienten oder die öffentliche Gesundheit ….

EFSA Assessment (Beispiel)

European Food Safety Authority

EFSA Journal 2013;11(10):3412

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to hydroxyanthracene derivatives and improvement of bowel function pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

The Panel concludes that a cause and effect relationship has been established between consumption of hydroxyanthracene derivatives and improvement of bowel function.

The Panel considers that the following wording reflects the scientific evidence: "Hydroxyanthracene derivatives improve bowel function".

The Panel considers that in order to bear the claim, a product should provide 10 mg hydroxyanthracene derivatives per day either from the root and rhizome of *Rheum palmatum* L. and/or *Rheum officinale* Baillon and/or their hybrids, and/or from the leaves or fruits of *Cassia senna* L. and/or *Cassia angustifolia* Vahl, and/or from the bark of *Rhamnus frangula L* and/or from the bark of *Rhamnus purshianus* D.C. and/or from *Aloe barbadensis* Miller and/or various aloe species, mainly *Aloe ferox* Miller and its hybrids. The target population is adults.

In relation to the restrictions of use, the Panel notes that stimulant laxatives should not be consumed continually for periods longer than one to two weeks. The use of stimulant laxatives for more than two weeks requires medical supervision. Long-term use of stimulant laxatives should be avoided owing to the danger of electrolyte imbalance, impaired function of the intestine, and dependence on laxatives. Stimulant laxatives should only be used if an effect on bowel function cannot be achieved by a change of diet or the administration of bulk forming agents.

EFSA Assessment (Beispiel)

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 22 November 2017

doi: 10.2903/j.efsa.2018.5090

Safety of hydroxyanthracene derivatives for use in food

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS),
Maged Younes, Peter Aggett, Fernando Aguilar, Riccardo Crebelli, Metka Filipič,
Maria Jose Frutos, Pierre Galtier, David Gott, Ursula Gundert-Remy, Gunter Georg Kuhnle,
Claude Lambré, Jean-Charles Leblanc, Inger Therese Lillegaard, Peter Moldeus,
Alicja Mortensen, Agneta Oskarsson, Ivan Stankovic, Ine Waalkens-Berendsen,
Rudolf Antonius Woutersen, Raul J Andrade, Cristina Fortes, Pasquale Mosesso,
Patrizia Restani, Fabiola Pizzo, Camilla Smeraldi, Adamantia Papaioannou and Matthew Wright

Epidemiological data suggested an increased risk for colorectal cancer associated with the general use of laxatives, several of which contain hydroxyanthracene derivatives.

Five cohort studies were reviewed by the Panel and an increased risk for colorectal cancer was found in all, however, only in two studies the results were statistically significant. Based on the studies reviewed by the European Medicines Agency (EMA) and the results of more recent large epidemiological studies, the Panel agreed with previous evaluations that the prolonged use of laxatives is a possible risk factor for colorectal cancer. Nevertheless, the Panel was of the view that better designed epidemiological studies (e.g. cohort studies with large sample size and proper control for confounding factors) that investigate the relationship between anthranoids laxatives use and colorectal are needed.

Based on the data currently available, the Panel concluded that hydroxyanthracene derivatives should be regarded as genotoxic and carcinogenic unless there are specific data to the contrary, such as for rhein and that there is a safety concern for extracts containing hydroxyanthracene derivatives although uncertainty persists.

Furthermore, the Panel was unable to provide advice on a daily intake of hydroxyanthracene derivatives that does not give rise to concerns about harmful effects to health, for the general population, and as appropriate, for vulnerable subgroups of the population.

HMPC Assessment (Beispiel)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 November 2016
EMA/HMPC/625788/2015
Committee on Herbal Medicinal Products (HMPC)

European Union herbal monograph on *Aloe barbadensis* Mill. and on *Aloe* (various species, mainly *Aloe ferox* Mill. and its hybrids), folii succus siccatus

Final

Initial assessment	
Discussion in Working Party on European Union monographs and European Union list (MLWP)	January 2006 March 2006
Adoption by Committee on Herbal Medicinal Products (HMPC) for release for consultation	3 March 2006
End of consultation (deadline for comments)	30 June 2006
Re-discussion in MLWP	September 2006
Adoption by HMPC	7 September 2006
First systematic review	
Discussion in Working Party on European Union monographs and list (MLWP)	September 2015 November 2015 February 2016 April 2016 May/June 2016 September 2016
Adoption by HMPC	22 November 2016

Keywords	Herbal medicinal products; HMPC; European Union herbal monographs; well-established medicinal use; barbados aloes; *Aloe barbadensis* Mill.; cape aloes; *Aloe* (mainly *Aloe ferox* Mill. and its hybrids)

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HMPC Assessment (Beispiel)

4. Clinical particulars

4.1. Therapeutic indications

Well-established use	Traditional use
Herbal medicinal product for short-term use in cases of occasional constipation.	

4.2. Posology and method of administration

Well-established use	Traditional use
Posology *Adolescents over 12 years of age, adults, elderly* Single dose: Herbal preparation equivalent to 10 – 30 mg hydroxyanthracene derivatives, calculated as aloin, to be taken once daily at night. The correct individual dose is the smallest required to produce a comfortable soft-formed motion. The use in children under 12 years of age is contraindicated (see section 4.3 Contraindications). The pharmaceutical form must allow lower dosages. **Duration of use** Not to be used for more than 1 week. Usually it is sufficient to take this medicinal product up to two to three times during that week. If the symptoms persist during the use of the medicinal product, a doctor or a pharmacist should be consulted. See also section 4.4 Special warnings and precautions for use.	

HMPC Assessment (Beispiel)

4.3. Contraindications

Well-established use	Traditional use
Hypersensitivity to the active substance.	

European Union herbal monograph on *Aloe barbadensis* Mill. and on *Aloe* (various species, mainly *Aloe ferox* Mill. and its hybrids), folii succus siccatus
EMA/HMPC/625788/2015 Page 4/9

Well-established use	Traditional use
Cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory bowel diseases (e.g. Crohn's disease, ulcerative colitis), abdominal pain of unknown origin, severe dehydration state with water and electrolyte depletion. Pregnancy and lactation (see section 4.6 and 5.3) Children under 12 years of age.	

HMPC Assessment (Beispiel)

4.4. Special warnings and precautions for use

Well-established use	Traditional use
Long-term use of stimulant laxatives should be avoided, as use for more than a brief period of treatment may lead to impaired function of the intestine and dependence on laxatives. If laxatives are needed every day the cause of the constipation should be investigated. Aloe preparations should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents. Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, adrenocorticosteroids or liquorice root, have to consult a doctor before taking aloes concomitantly. Like all laxatives, aloes should not be taken by patients suffering from faecal impaction and undiagnosed, acute or persistent gastro-intestinal complaints, e.g. abdominal pain, nausea and vomiting unless advised by a doctor because these symptoms can be signs of potential or existing intestinal blockage (ileus). Patients with kidney disorders should be aware of possible electrolyte imbalance. If the symptoms worsen during the use of the medicinal product, a doctor or a pharmacist should be consulted.	

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EMA

Quelle: SpiegelOnline vom 26.01.2019: „Europäische Arzneimittel-Agentur schließt Büros in London"

- koordiniert Bewertung und Überwachung aller Human- und Tierarzneimittel
- seit 1995
- größter Teil der Arbeit durch verschiedene Komitees durchgeführt
- mehr als 4500 Experten
- zentrale Arzneimittel-Datenbanken (EudraCT; EudraVigilance; EudraPharm; EudraGMP; European Public Assessment Report)

EMA

Committee for Medicinal Products for Human Use (CHMP) (1995; until 2004 CPMP)

Committee for Medicinal Products for Veterinary Use (CVMP) (1995)

Committee for Orphan Medicinal Products (COMP) (2000)

Committee on Herbal Medicinal Products (HMPC) (2004)

Paediatric Committee (PDCO) (2006)

Committee for Advanced Therapies (CAT) (2007)

Pharmacovigilance Risk Assessment Committee (PRAC) (2012)

HMPC

Composition

Chair and Vice Chair

+

1 member/Member State

+

1 member each from Norway and Iceland (EFTA states)

+

max. 5 co-opted members

+

accompanied by experts, observers (e.g. EDQM)

Clinical pharmacology

Experimental/non-clinical pharmacology

Toxicology

Paediatric medicine

General and family medicine

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WEU

„allgemein medizinisch verwendet“

Nachweis:

- Zeitraum, über den ein Stoff verwendet wurde (nicht kürzer als ein Jahrzehnt, nachdem der betreffende Stoff erstmals systematisch und dokumentiert in der Gemeinschaft als Arzneimittel verwendet wurde)
- quantitative Aspekte der Verwendung des Stoffes
- Ausmaß des wissenschaftlichen Interesses an der Verwendung des Stoffes (das aus den dazu erschienenen wissenschaftlichen Veröffentlichungen hervorgeht)
- Einheitlichkeit der wissenschaftlichen Beurteilung

§ 22 Abs. 3 AMG:
An Stelle der Ergebnisse nach Absatz 2 Nr. 2 und 3 kann anderes wissenschaftliches Erkenntnismaterial vorgelegt werden, und zwar
1. bei einem Arzneimittel, dessen Wirkstoffe seit mindestens zehn Jahren in der Europäischen Union allgemein medizinisch … verwendet wurden, deren Wirkungen und Nebenwirkungen bekannt und aus dem wissenschaftlichen Erkenntnismaterial ersichtlich sind …

TRAD (§ 39b-d AMG)

- AM zum Zeitpunkt der Antragstellung seit mindestens 30 Jahren, davon mindestens 15 Jahre in der Gemeinschaft, medizinisch verwendet
- ohne ärztliche Aufsicht in Hinblick auf die Stellung einer Diagnose, die Verschreibung oder die Überwachung angewendet
- bestimmte Stärke und Dosierung
- nur oral, äußerlich und/oder zur Inhalation
- **unter den angegebenen Anwendungsbedingungen unschädlich**
- **pharmakologische Wirkungen oder Wirksamkeit aufgrund langjähriger Anwendung und Erfahrung plausibel**

Regulatorische Hintergründe u.a.

- AM, die älter sind als die nationale und europäische Arzneimittelgesetzgebung
- viele trad. AM werden den Anforderungen eines regulären Zulassungsverfahrens nicht gerecht

CHMP

The Committee for Medicinal Products for Human Use (CHMP) establishes a number of working parties ... These working parties have expertise in a particular scientific field, and are composed of members selected from the list of European experts maintained by the Agency.

The current CHMP standing working parties are:

Healthcare Professionals' Working Party
Biologics Working Party
Patients' and Consumers' Working Party
Quality Working Party
Safety Working Party
Scientific Advice Working Party

SWP

The Safety Working Party (SWP) provides recommendations to the Committee for Medicinal Products for Human Use (CHMP) **on all matters relating directly or indirectly to non-clinical aspects of safety**. Its work includes:

- providing support to dossier evaluation;
- **assessing non-clinical safety findings**;
- providing training on non-clinical safety assessments;
- **providing advice**, through the CHMP, **on non-clinical-safety-related matters** to the European Commission, the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMD(h)) and **the Committee on Herbal Medicinal Products (HMPC)**;
- liaising with interested parties;
- **contributing to international co-operation**.

Estragol – bisherige Bewertungen

- **SCF (Scientific Committee on Food) 2001:**

Opinion of the Scientific Committee on Food on Estragole (1-allyl-4-methoxybenzene). SCF/CS/FLAV/FLAVOUR/6 ADD 2 Final, 26.09.2001.

> „*Estragole has been demonstrated to be genotoxic and carcinogenic. Therefore the existence of a threshold cannot be assumed and the Committee could not establish a safe exposure limit. Consequently, reductons in exposure and restrictions in use levels are indicated.“*

- **CoE (Council of Europe) 2005:**

Estragole. in: Active principles (constituents of toxicological concern) contained in natural sources of flavouring. 2005, 76-86

> *“… Estragole was classified by the Committee of experts at its 36th meeting as a week genotoxic carcinogen. Therefore the Committee of experts concluded at its 48th meeting to classify as a type T active principle, for which no (T)MDI can be set. …. Efforts should be made to reduce the amount of estragole in food as far as possible. ….”*

Estragol – bisherige Bewertungen

- **HMPC 2005:**

Public statement on the use of herbal medicinal products containing Estragole (EMA/HMPC/137212/2005)

"…. It is concluded that the present exposure to estragole resulting from consumption of herbal medicinal products (short time use in adults at recommended posology) does not pose a significant cancer risk. Nevertheless, further studies are needed to define both the nature and implications of the dose-response curve in rats at low levels of exposure to estragole. In the meantime exposure of estragole to sensitive groups such as young children, pregnant and breastfeeding woman should be minimized."

Estragol – bisherige Bewertungen

- **EFSA 2009:**

ESCO Report "Advice on the EFSA guidance document for the safety assessment of botanicals and botanical preparations intended for use as food supplements, based on real case studies." EFSA Journal 2009; 7(9):280)

"Using the BMDL10 values of 9 to 33 mg/kg/day for female mice as derived from Miller et al study (Miller et al., 1983) … one can calculate a MOE of about 34 to 1000 which indicates that use of bitter fennel fruits for preparation of fennel tea could be considered a high priority for risk management.

…

From these examples it becomes clear that when a matrix effect is advocated to support the safety of a botanical or a botanical ingredient, experimental data and/or other data need to be provided that support the occurrence of the matrix effect in vivo at relevant levels of intake and with botanicals or botanical preparations of interest."

Estragol – bisherige Bewertungen

- **Regulation No 1334/2008:**
  - *Verbot vom Zusatz von Estragol in Lebensmittel (ab 2011 in Kraft)*
  - *Höchstmengen für Estragol, die aus der Verwendung von Aromen und/oder Lebensmittelzutaten resultieren, die natürlicherweise diese Substanz enthalten*

Teil B: Höchstmengen bestimmter Stoffe, die von Natur aus in Aromen und Lebensmittelzutaten mit Aromaeigenschaften vorkommen, in bestimmten zusammengesetzten Lebensmitteln, denen Aromen und/oder Lebensmittelzutaten mit Aromaeigenschaften zugesetzt worden sind

Bezeichnung des Stoffes	Zusammengesetzte Lebensmittel, in denen die Menge dieses Stoffes eingeschränkt ist	Höchstmenge mg/kg
Beta-Asaron	Alkoholische Getränke	1,0
1-Allyl-4-methoxybenzol Estragol (1)	Milcherzeugnisse	50
	Verarbeitetes Obst und Gemüse (einschließlich Pilze, Wurzelgemüse, Knollen, Hülsenfrüchte, Leguminosen), verarbeitete Nüsse und Samen	50
	Fischerzeugnisse	50
	Alkoholfreie Getränke	10

(1) Die Höchstwerte gelten nicht, wenn ein zusammengesetztes Lebensmittel keine hinzugefügten Aromen enthält und die einzigen Lebensmittelzutaten mit Aromaeigenschaften, die hinzugefügt wurden, frische, getrocknete oder tiefgekühlte Kräuter oder Gewürze sind. Die Kommission schlägt gegebenenfalls Änderungen zu dieser Ausnahme nach Konsultation der Mitgliedstaaten und der Behörde auf der Grundlage der durch die Mitgliedstaaten bereitgestellten Daten und der neuesten wissenschaftlichen Erkenntnisse und unter Berücksichtigung der Verwendung von Kräutern, Gewürzen und natürlichen Armomaextrakten vor.

„Established rules of scientific assessment“ of risks?

GUIDANCE

EFSA Journal

ADOPTED: 17 November 2016

doi: 10.2903/j.efsa.2017.4658

Update: use of the benchmark dose approach in risk assessment

EFSA Scientific Committee,
Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Katrine Helle Knutsen, Simon More, Alicja Mortensen, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci, Guido Rychen, Vittorio Silano, Roland Solecki, Dominique Turck, Marc Aerts, Laurent Bodin, Allen Davis, Lutz Edler, Ursula Gundert-Remy, Salomon Sand, Wout Slob, Bernard Bottex, Jose Cortinas Abrahantes, Daniele Court Marques, George Kass and Josef R. Schlatter

Abstract

The Scientific Committee (SC) reconfirms that the benchmark dose (BMD) approach is a scientifically more advanced method compared to the NOAEL approach for deriving a Reference Point (RP). Most of the modifications made to the SC guidance of 2009 concern the section providing guidance on how to apply the BMD approach. Model averaging is recommended as the preferred method for calculating the BMD confidence interval, while acknowledging that the respective tools are still under development and may not be easily accessible to all. Therefore, selecting or rejecting models is still considered as a suboptimal alternative. The set of default models to be used for BMD analysis has been reviewed, and the Akaike information criterion (AIC) has been introduced instead of the log-likelihood to characterise the goodness of fit of different mathematical models to a dose-response data set. A flowchart has also been inserted in this update to guide the reader step-by-step when performing a BMD analysis, as well as a chapter on the distributional part of dose-response models and a template for reporting a BMD analysis in a complete and transparent manner. Finally, it is recommended to always report the BMD confidence interval rather than the value of the BMD. The lower bound (BMDL) is needed as a potential RP, and the upper bound (BMDU) is needed for establishing the BMDU/BMDL per ratio reflecting the uncertainty in the BMD estimate. This updated guidance does not call for a general re-evaluation of previous assessments where the NOAEL approach or the BMD approach as described in the 2009 SC guidance was used, in particular when the exposure is clearly smaller (e.g. more than one order of magnitude) than the health-based guidance value. Finally, the SC firmly reiterates to reconsider test guidelines given the expected wide application of the BMD approach.

Keywords: benchmark dose, BMD, BMDL, benchmark response, NOAEL, dose-response modelling, BMD software

Requestor: EFSA

Question number: EFSA-Q-2014-00747

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„ …. **Model averaging** is recommended as the preferred method for calculating the **BMD confidence interval**, while acknowledging **that the respective tools are still under development and may not be easily accessible to all**. ….“

Aber:

- *Einigkeit in Wissenschaft über die Durchführung/Parameter des BMD modelling?*

  z.B.

  - *Vergleich EFSA vrs. US EPA**
  - *Homepage EFSA zum EFSA-Workshop zu Benchmark-Dosis (01./02.03.2017):*
    *„Der Workshop soll den Bekanntheitsgrad der aktualisierten EFSA-Leitlinien erhöhen … Außerdem soll er – in Europa und darüber hinaus – zu einem zunehmend gemeinsamen Verständnis im Hinblick auf den BMD-Ansatz und dessen harmonisierte Anwendung beitragen.“ ***

**Haber et al. (2018), „Benchmark dose (BMD) modeling: current practice, issues, and challenges“, Critical Reviews in Toxicology, 48:5, 387-415*
**EFSA-Homepage: https://www.efsa.europa.eu/de/press/news/170124

(Pflanzliche) Arzneimittel

Grundlage ist das Arzneimittelgesetz (AMG)

§26 Arzneimittelprüfrichtlinien

1) Das Bundesministerium wird ermächtigt, durch Rechtsverordnung mit Zustimmung des Bundesrates Anforderungen an die in den §§ 22 bis 24 …. bezeichneten Angaben, Unterlagen und Gutachten sowie deren Prüfung durch die zuständige Bundesoberbehörde zu regeln. Die Vorschriften müssen dem jeweils gesicherten Stand der wissenschaftlichen Erkenntnisse entsprechen und sind laufend an diesen anzupassen, insbesondere sind Tierversuche durch andere Prüfverfahren zu ersetzen, wenn dies nach dem Stand der wissenschaftlichen Erkenntnisse im Hinblick auf den Prüfungszweck vertretbar ist. …

Arzneimittelprüfrichtlinie

Verordnung zur Anwendung der Arzneimittelprüfrichtlinien (Arzneimittelprüfrichtlinien-Verordnung - AMPV)

AMPV

Ausfertigungsdatum: 08.01.2016

Vollzitat:

"Arzneimittelprüfrichtlinien-Verordnung vom 8. Januar 2016 (BGBl. I S. 47)"

* Diese Verordnung dient der Umsetzung des Anhangs I der Richtlinie 2001/83/EG des Europäischen Parlaments und des Rates vom 6. November 2001 zur Schaffung eines Gemeinschaftskodexes für Humanarzneimittel (ABl. L 311 vom 28.11.2001, S. 67), die zuletzt durch die Richtlinie 2012/26/EU (ABl. L 299 vom 27.10.2012, S. 1) geändert worden ist.

Fußnote

```
(+++ Textnachweis ab: 16.1.2016 +++)
(+++ Amtlicher Hinweis des Normgebers auf EG-Recht:
     Umsetzung der
       EURL 83/2001            (CELEX Nr: 32001L0083) +++)
```

Eingangsformel

Auf Grund des § 26 Absatz 1 des Arzneimittelgesetzes, der zuletzt durch Artikel 52 Nummer 5 der Verordnung vom 31. August 2015 (BGBl. I S. 1474) geändert worden ist, verordnet das Bundesministerium für Gesundheit im Einvernehmen mit dem Bundesministerium für Umwelt, Naturschutz, Bau und Reaktorsicherheit:

§ 1 Anforderungen an einzureichende Unterlagen

Die Angaben, Unterlagen und Gutachten, die nach den §§ 22 bis 24 des Arzneimittelgesetzes, auch in Verbindung mit § 38 Absatz 2 und § 39b Absatz 1 des Arzneimittelgesetzes, bei der nach § 77 Absatz 1 oder Absatz 2 des Arzneimittelgesetzes zuständigen Bundesoberbehörde einzureichen sind, müssen die Anforderungen erfüllen, die in Anhang I Teil I bis III der Richtlinie 2001/83/EG des Europäischen Parlaments und des Rates vom 6. November 2001 zur Schaffung eines Gemeinschaftskodexes für Humanarzneimittel (ABl. L 311 vom 28.11.2001, S. 67) in der jeweils geltenden Fassung geregelt sind.

Direktive 2001/83/EG Anhang I

(2) The particulars and documents shall be presented as five modules: Module 1 provides European Community specific administrative data; Module 2 provides quality, non-clinical and clinical summaries, Module 3 provides chemical, pharmaceutical and biological information, Module 4 provides non-clinical reports and Module 5 provides clinical study reports. This presentation implements a common format for all ICH ([1]) regions (European Community, United States of America, Japan). These five Modules shall be presented in strict accordance with the format, content and numbering system delineated in details in Volume 2 B of the Notice to Applicants referred to above.

(3) The European Community-CTD-presentation is applicable for all types of marketing authorisation applications irrespective of the procedure to be applied (i.e. centralised, mutual recognition or national) and of whether they are based on a full or abridged application. It is also applicable for all types of products including new chemical entities (NCE), radio-pharmaceuticals, plasma derivatives, vaccines, herbal medicinal products, etc.

(4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and published by the European Medicine Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.

ICH M7(R1)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 August 2015
EMA/CHMP/ICH/83812/2013
Committee for Human Medicinal Products

ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk
Step 5

Transmission to CHMP	July 2017
Adoption by CHMP for release for consultation	July 2017
End of consultation (deadline for comments)	January 2018
Final adoption by CHMP	February 2018
Date for coming into effect	February 2018

7. Risk characterization

As a result of hazard assessment described in Section 6, each impurity will be assigned to one of the five classes in Table 1. For impurities belonging in Classes 1, 2, and 3 the principles of risk characterization used to derive acceptable intakes are described in this section.

7.1. TTC-based acceptable intakes

A TTC-based acceptable intake of a mutagenic impurity of 1.5 µg per person per day is considered to be associated with a negligible risk (theoretical excess cancer risk of <1 in 100,000 over a lifetime of exposure) and can in general be used for most pharmaceuticals as a default to derive an acceptable limit for control. This approach would usually be used for mutagenic impurities present in pharmaceuticals for long-term treatment (> 10 years) and where no carcinogenicity data are available (Classes 2 and 3).

7.2. Acceptable intakes based on compound-specific risk assessments

7.2.1. Mutagenic impurities with positive carcinogenicity data (class 1 in table 1)

Compound-specific risk assessments to derive acceptable intakes should be applied instead of the TTC-based acceptable intakes where sufficient carcinogenicity data exist. For a known mutagenic carcinogen, a compound-specific acceptable intake can be calculated based on carcinogenic potency and linear extrapolation as a default approach. Alternatively, other established risk assessment practices such as those used by international regulatory bodies may be applied either to calculate acceptable intakes or to use already existing values published by regulatory authorities (Note 4).

ICH M7(R1)

Note 4 Example of linear extrapolation from the TD_{50}

It is possible to calculate a compound-specific acceptable intake based on rodent carcinogenicity potency data such as TD_{50} values (doses giving a 50% tumor incidence equivalent to a cancer risk probability level of 1:2). Linear extrapolation to a probability of 1 in 100,000 (i.e., the accepted lifetime risk level used) is achieved by simply dividing the TD_{50} by 50,000. This procedure is similar to that employed for derivation of the TTC.

Calculation example: Ethylene oxide

TD_{50} values for ethylene oxide according to the Carcinogenic Potency Database are 21.3 mg/kg body weight/day (rat) and 63.7 mg/kg body weight/day (mouse). For the calculation of an acceptable intake, the lower (i.e., more conservative) value of the rat is used.

To derive a dose to cause tumors in 1 in 100,000 animals, divide by 50,000:

21.3 mg/kg ÷ 50,000 = 0.42 µg/kg

To derive a total human daily dose:

0.42 µg/kg/day x 50 kg body weight = 21.3 µg/person/day

Hence, a daily life-long intake of 21.3 µg ethylene oxide would correspond to a theoretical cancer risk of 10^{-5} and therefore be an acceptable intake when present as an impurity in a drug substance.

Alternative methods and published regulatory limits for cancer risk assessment

The Carcinogenic Potency Project

Estragole (CAS 140-67-0)

SMILES, InChI and Structure are below.

Rats and Mice: Cancer Test Summary

Rat Target Sites		Mouse Target Sites		TD_{50} (mg/kg/day)	
Male	Female	Male	Female	Rat	Mouse
no test	no test	no test	liv	no test	51.8

Key to the Table Above

Positivity: For each chemical with a positive (carcinogenic) experiment in the Carcinogenic Potency Database (CPDB), results are included on carcinogenic potency (TD_{50}) in each species and target sites in males and females. Positivity is determined by an author's opinion in a published paper. If all experimental results in the CDPB are negative in a sex-species group, "no positive" appears. If the CPDB has no experiments in the sex-species group, "no test" appears. The summary presents the strongest evidence of carcinogenicity in each group. If there are both positive and negative experiments in a sex-species, the negative results are ignored in this Summary Table.

Target Site Codes: liv = liver. Target sites are listed if any author of published experimental results concluded that tumors were induced in that organ by the test agent. If there is more than one positive experiment in a sex-species, target sites listed may be from more than one experiment, e.g. if liver and lung are both listed, then liver may have been a target in one experiment and lung in another.

TD_{50}: Our standardized measure of carcinogenic potency, TD_{50}, is the daily dose rate in mg/kg body weight/day to induce tumors in half of test animals that would have remained tumor-free at zero dose. Whenever there is more than one positive experiment in a species, the reported TD_{50} value is a Harmonic Mean calculated using the TD_{50} value from the most potent target site in each positive experiment.

The Carcinogenic Potency Database (CPDB) is a unique and widely used international resource of the results of 6540 chronic, long-term animal cancer tests on 1547 chemicals. The CPDB provides easy access to the bioassay literature, with qualitative and quantitative analyses of both positive and negative experiments that have been published over the past 50 years in the general literature through 2001 and by the National Cancer Institute/National Toxicology Program through 2004. The CPDB standardizes the diverse literature of cancer bioassays that vary widely in protocol, histopathological examination and nomenclature, and in the published author's choices of what information to provide in their papers. Results are reported in the CPDB for tests in rats, mice, hamsters, dogs, and nonhuman primates.

For each experiment, information is included on species, strain, and sex of test animal; features of experimental protocol such as route of administration, duration of dosing, dose level(s) in mg/kg body weight/day, and duration of experiment; experimental results are provided on target organ, tumor type, and tumor incidence; carcinogenic potency (TD_{50}) and its statistical significance; shape of the dose-response, author's opinion as to carcinogenicity, and literature citation.

Only tests with dosing for at least ¼ the standard lifespan of the species and experiment length at least ½ the lifespan are included in the CPDB. Only routes of administration with whole body exposure are included. Doses are standardized, average dose rates in mg/kg/day. A description of methods used in the CPDB to standardize the diverse literature of animal cancer tests is presented for: 1) Criteria for inclusion of experiments 2) Standardization of average daily dose levels and 3) TD_{50} estimation for a standard lifespan. See Methods for other details.

TD_{50} provides a standardized quantitative measure that can be used for comparisons and analyses of many issues in carcinogenesis. The range of TD_{50} values across chemicals that are rodent carcinogens is more than 100 million-fold. More than half the chemicals tested are positive in at least one experiment.

A plot of all results on each experiment in the CPDB for this chemical is presented below. These results are the source information for the Cancer Test Summary table above.

Estragol – mögliche Grenzwerte

- **Carcinogenic Potency Project: 51 mg/kg/Tag**

✓ 51 mg/kg/Tag ÷ 50 000 = 1,02 µg/kg/Tag

✓ 1,02 µg/kg/Tag x 50 kg KG = **51 µg/Tag**

ICH M7(R1)

Hence, a daily life-long intake of 21.3 µg ethylene oxide would correspond to a theoretical cancer risk of 10^{-5} and therefore be an acceptable intake when present as an impurity in a drug substance.

Alternative methods and published regulatory limits for cancer risk assessment

As an alternative of using the most conservative TD50 value from rodent carcinogenicity studies irrespective of its relevance to humans, an in-depth toxicological expert assessment of the available carcinogenicity data can be done in order to initially identify the findings (species, organ, etc.) with highest relevance to human risk assessment as a basis for deriving a reference point for linear extrapolation. Also, in order to better take into account directly the shape of the dose-response curve, a benchmark dose such as a benchmark dose lower confidence limit 10% (BMDL10, an estimate of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodents) may be used instead of TD50 values as a numerical index for carcinogenic potency. Linear extrapolation to a probability of 1 in 100,000 (i.e., the accepted lifetime risk level used) is then achieved by simply dividing the BMDL10 by 10,000.

Compound-specific acceptable intakes can also be derived from published recommended values from internationally recognized bodies such as World Health Organization (WHO, International Program on Chemical Safety [IPCS] Cancer Risk Assessment Programme) and others using the appropriate 10-5 lifetime risk level. In general, a regulatory limit that is applied should be based on the most current and scientifically supported data and/or methodology.

Estragol – $BMDL_{10}$

Table 9: Overview of the data from Miller et al. (1983) on the incidence of hepatomas in female mice exposed for 12 months via the diet to estragole

dose	Estimated dose mg/kg bw/day	No of animals	No of mice with hepatomas	incidence
0	0	43	0	0
0.23% in diet	150-300	48	27	56
0.46% in diet	300-600	49	35	71

*ESCO Report "Advice on the EFSA guidance document for the safety assessment of botanicals and botanical preparations intended for use as food supplements, based on real case studies" (EFSA Journal 2009; 7(9):280)
** van den Berg et al. Levels of genotoxic and carcinogenic compounds in plant food supplements and associated risk assessment. Food and Nutrition Sciences, 2011, 2, 989-1010

in EFSA*: $BMDL_{10}$ = zwischen 9 und 33 mg/kg/Tag
in van den Berg *et al.* **: $BMDL_{10}$ = zwischen 3,3 und 6,5 mg/kg/Tag

Vorsicht: Studiendesign = Estragol an 3 Tagen/Wochen über 12 Monate!!

NTP, 2011 – Eignung? (3 Monatsstudie)

Estragol – mögliche Grenzwerte

- **Carcinogenic Potency Project: 51 mg/kg/Tag**

✓ 51 mg/kg/Tag ÷ 50 000 = 1,02 µg/kg/Tag

✓ 1,02 µg/kg/Tag x 50 kg KG = **51 µg/Tag**

- **$BMDL_{10}$: 3,3-33 mg/kg/Tag**

✓ 3,3-33 mg/kg/Tag ÷ 10 000 = 0,33-3,3 µg/kg/Tag

✓ 0,33-3,3 µg/kg/Tag x 50 kg KG = **16,5-165 µg/Tag**

ICH M7(R1)

7.2.2. Mutagenic impurities with evidence for a practical threshold

The existence of mechanisms leading to a dose response that is non-linear or has a practical threshold is increasingly recognized, not only for compounds that interact with non-DNA targets but also for DNA-reactive compounds, whose effects may be modulated by, for example, rapid detoxification before coming into contact with DNA, or by effective repair of induced damage. The regulatory approach to such compounds can be based on the identification of a No-Observed Effect Level (NOEL) and use of uncertainty factors (see ICH Q3C(R5), Ref. 7) to calculate a permissible daily exposure (PDE) when data are available.

Estragol – nach ICH Q3C

LOAEL = 37,5 mg/kg (NTP, 2011)

$$\text{PDE} = \frac{37{,}5\ \text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}\text{(LOEL)} \times 50\ \text{kg (weight adjustment)}}{5\ (F1) \times 10\ (F2) \times 5\ (F3) \times 10\ (F4) \times 10\ (F5)} = 0{,}075\ \text{mg/day}$$

F1 = 5 for extrapolation from rats to humans
F2 = 10 to account for variability between individuals
F3 = 5 for study duration of at least 3 months in rodents
F4 = 10 for severe toxicity (allowing an assumption that the toxicity has a practical threshold)
F5 = 10 because LOAEL was determined

Estragol – mögliche Grenzwerte

- **Carcinogenic Potency Project: 51 mg/kg/Tag**

✓ 51 mg/kg/Tag ÷ 50 000 = 1,02 µg/kg/Tag

✓ 1,02 µg/kg/Tag x 50 kg KG = **51 µg/Tag**

- **$BMDL_{10}$: 3,3-33 mg/kg/Tag**

✓ 3,3-33 mg/kg/Tag ÷ 10 000 = 0,33-3,3 µg/kg/Tag

✓ 0,33-3,3 µg/kg/Tag x 50 kg KG = **16,5-165 µg/Tag**

- **ICH Q3C: 75 µg/Tag**

Estragol – weitere Studien

Paini *et al*. (2010, 2012)

- 2010: formation of DNA adducts in the liver of male rats on the basis of in vitro incubations with rat hepatocytes exposed to estragole; **predicts that formation of the principal adduct in rat liver is linear up to at least 100 mg/kg**
- 2012: dose-dependent estragole-DNA adduct formation in rat liver + the urinary excretion of 1'-hydroxyestragole glucuronide in male rats (n=10, per group) (0, 5, 30, 75, 150, 300 mg estragole/kg)

Suzuki *et al*. (2012a, 2012b)

- dose-dependent adduct formation in rats and mice respectively
- doses: 22 to 600 mg/kg
- statistically significant increases in adduct formation only found at the higher doses, liver adducts were formed also at the lowest doses assayed
- it suggests that DNA adduct formation takes place also at relatively low concentrations

Estragol – mögliche Grenzwerte

- **Carcinogenic Potency Project: 51 mg/kg/Tag**

✓ 51 mg/kg/Tag ÷ 50 000 = 1,02 µg/kg/Tag

✓ 1,02 µg/kg/Tag x 50 kg KG = **51 µg/Tag**

- **$BMDL_{10}$: 3,3-33 mg/kg/Tag**

✓ 3,3-33 mg/kg/Tag ÷ 10 000 = 0,33-3,3 µg/kg/Tag

✓ 0,33-3,3 µg/kg/Tag x 50 kg KG = **16,5-165 µg/Tag**

- **ICH Q3C: 75 µg/Tag**

Estragol – was fehlt?

- ✓ aktuelle Berechnungen zur Aufnahme von Estragol durch die Nahrung (CoE 2005: “total intake from all sources to be in order of 1 mg/person/ day” – gilt das auch noch für 2019?)
- ✓ epidemiologische Daten (?)
- ✓ Daten zur Linearität / Nicht-Linearität (in niedrigen Dosierungen)
- ✓ Untersuchungen zu Matrixefekten / Studien mit pfl. Zubereitungen (?)
- ✓ gute Studien zur Karzinogenität (Studiendesign)
- ✓ abgestimmte Bewertungen (?)

Vielen Dank für Ihre Aufmerksamkeit!

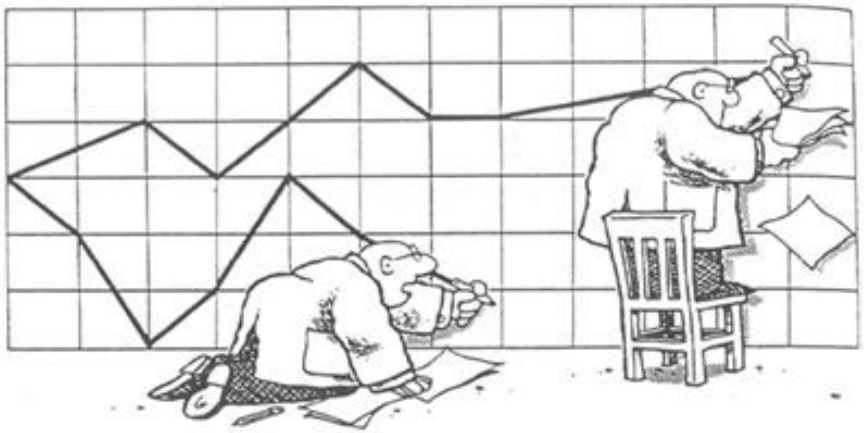

FIGURE 2.3 SOURCE: *National Wildlife Magazine*, August–September, 1984. Copyright © 1984 Mark Taylor. Reprinted with permission of Mark Taylor.

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