



LEIBNIZ RESEARCH CENTRE
FOR WORKING ENVIRONMENT
AND HUMAN FACTORS

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BfR Symposium „50 Jahre Kosmetik-Kommission: Wissenschaft im Dienste des Verbraucherschutzes“ 16. Oktober 2018, Berlin

Endokrin aktive Substanzen in Sonnenschutzmitteln

Gisela H. Degen

Member of **SCCP / SCCS** (2004 – 2016); Chair of WP CosIng (2015-2016)
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OUTLINE

✧ Endokrin Aktive Substanz / Endokriner Disruptor *

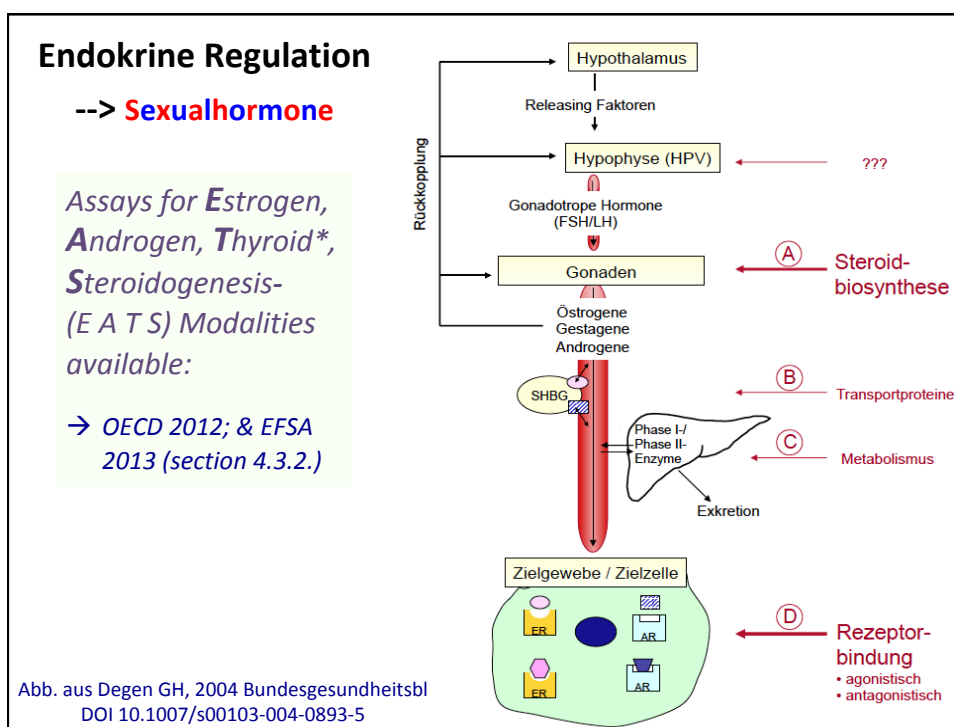
- Definitionen (EAS or ED ?)
- Wirkmodus (Mode of Action)
- Regulation: *Hazard- vs. Risk-based*
- EAS in Sonnenschutzmitteln
- **UV Filter**
- **Konservierungsmittel**

✧ Diskussion - Ausblick

- ✧ Risikokommunikation: *EAS oder ED ?*
- ✧ In vitro - in vivo Extrapolation

apologies for d-english

* Ein Sonderfall für die Bewertung ? !



Schilddrüse ...

REVIEW ARTICLE *Journal of Neuroendocrinology*, 2004, Vol. 16, 809–818

Timing of Thyroid Hormone Action in the Developing Brain: Clinical Observations and Experimental Findings

R. T. Zoeller* and J. Rovett†

REVIEW ARTICLE

Arch Toxicol
DOI 10.1007/s00204-016-1735-6

Assessing the potential impact on the thyroid axis of environmentally relevant food constituents/contaminants in humans

Gerhard Eisenbrand¹ · Heinz-Peter Gelbke²

Definitions

I

WHO/IPCS 2002

*“An **endocrine disrupter** is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes **adverse** health effects in an intact organism, or its progeny, or (sub)populations.”*

*“A **potential endocrine disrupter** is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations.*

→ an endocrine active substance [EAS]

Definitions

II

Adversity ?

“A change in morphology, physiology, growth, reproduction, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences”.

WHO/IPCS EHC 240, 2009

>> Interference with **components** of the endocrine system or **“endocrine disruption” is not a toxicological endpoint per se**, but one of the many **modes-of-action** which may result in adverse effects. *WHO Report 2002*

Endokrin aktive Substanzen: *Modes of Action*

a) Interaktion mit Hormon-Rezeptoren (*agonistic, antagonistic*)

Normal Endocrine Signaling

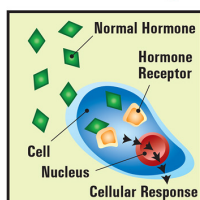


Fig. from Schug T et al. 2016

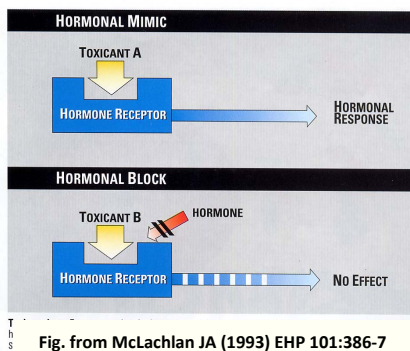


Fig. from McLachlan JA (1993) EHP 101:386-7

b) Interferenz mit Hormon-Biosynthese, Metabolismus oder Transport

e.g. Aromatase-Inhibitors, Enzyminductors, Thyroidperoxidase Inhibitors, Agents binding to SHBG or other transport proteins

Resultieren aus zellulären Effekten (a or b) auch funktionale Veränderungen in vivo ??

Pharmaceutical Drugs in Pregnancy: ‘proof of principal’ for Endocrine disruption

Aminogluthetimid

an *Aromatase Inhibitor*

→ Pseudohermaphroditism in Girls *

Danazol – potent *Androgen*;

at 200 mg or more

→ Virilisation in some female offspring **

Diethylstilbestrol

Highly potent *Estrogen* and *Anti-Androgen*

→ “DES-Daughters“
“DES-Sons“

CONCEPT: irreversible effects upon exposure in critical stages of development

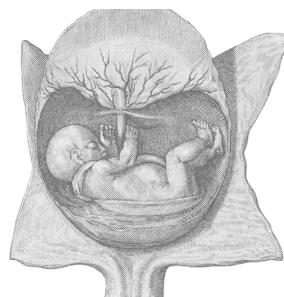



Abbildung aus

Fabricius ab Aquapendente, De Formato Foetu, 1624


Herzog August Bibliothek Wolfenbuettel

*LeMaire et al 1972 **Brunskill 1992 cited in Hotchkiss K et al. (2008)

<p>Regulatory ‘Arena’</p>  <p>Biocides, Plant Protection products, and REACH</p> <ul style="list-style-type: none"> <input type="checkbox"/> FOOD: Ingredients, Preservatives, Contaminants ... EFSA European Food Safety Authority <input type="checkbox"/> Non-Food: Cosmetics, Toys, etc. SCCS Scientific Committee for Consumer Safety <input type="checkbox"/> Occupation SCOEL SC for Occupational Exposure Limits <input type="checkbox"/> Environment SCHEER SC on Health, Environment & Emerging Risks 	<p>Potential Endocrine Disruptors</p> <div style="border: 1px solid black; padding: 5px; text-align: center;"> <p>scientific <i>criteria</i> for their identification ?</p> </div> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p><i>Examples: man-made / natural</i></p> <p><i>Bisphenol A</i> <i>Daidzein, Genistein</i> <i>Parabenes,</i> <i>Zearalenone</i></p> <p><i>Parabenes, org. UV Filter</i> <i>Phthalates</i> <i>‘Botanicals’</i></p> <p><i>Alkylphenols, Metals,</i> <i>Pharmaceuticals (OC) ...</i></p> <p><i>Tributylzinn; POPs;</i> <i>Drugs; ...</i></p> </div> <div style="border: 1px solid black; padding: 5px; margin-top: 10px; text-align: center;"> <p style="writing-mode: vertical-rl; transform: rotate(180deg);">Hazard or Risk Assessment ?</p> </div>
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EU Roadmap activities:
... need to harmonize guidance on the regulation of EDs

Arch Toxicol (2017) 91:1001–1006
DOI 10.1007/s00204-016-1866-9



MEETING REPORTS

Scientific principles for the identification of endocrine-disrupting chemicals: a consensus statement

Roland Solecki¹ · Andreas Kortenkamp² · Åke Bergman³ · Ibrahim Chahoud⁴ · Gisela H. Degen⁵ · Daniel Dietrich⁶ · Helmut Greim⁷ · Helen Håkansson⁸ · Ulla Hass⁹ · Trine Husoy¹⁰ · Miriam Jacobs¹¹ · Susan Jobling² · Alberto Mantovani¹² · Philip Marx-Stoelting¹ · Aldert Piersma¹³ · Vera Ritz¹ · Remy Slama¹⁴ · Ralf Stahlmann⁴ · Martin van den Berg¹⁵ · R. Thomas Zoeller¹⁶ · Alan R. Boobis¹⁷

“It is expected that the consensus reached will serve as an important basis for the development of regulatory ED criteria.”

* * * * *

Testai E, Galli C, Dekant W, Marinovich M, Piersma AH, Sharpe RM (2013)
A plea for risk assessment of endocrine disrupting chemicals. *Toxicology* 314: 51-59

Autrup H, Barile FA, Blauboer B, Degen GH, Dekant W, Dietrich D, et al. (2015)
Principles of pharmacology and toxicology govern also effects of chemicals on the endocrine system. *Toxicol Sci* 146: 11-15

Definitions WHO/IPCS

A **potential endocrine disruptor** is an exogenous substance or mixture that possesses *properties that might lead* to endocrine disruption in an intact organism or its progeny, or (sub)populations. → EAS

An **endocrine disruptor** is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes **adverse** health effects in an intact organism or its progeny, or (sub)populations. → ED

An ED defined by three criteria:

- i) an **adverse** effects in an intact organism or a (sub)population,
- ii) an **endocrine** activity, **and**
- iii) a plausible **causal relationship** between the two. (EFSA; JRC; SCCS)

“The challenge“

Number of Chemicals:

Testing for hazard „endocrine active“

Longterm-studies (Reprod./Devel. Tox) **are quite demanding ...** and no longer permitted for cosmetic ingredients

Prioritization / Safety assessment
Substances of importance ??
Exposure and potency matter

Exposition (engl. Exposure)

- **Womit ? Wie hoch ?**
Kosmetika, Nahrung, Pharmaka
- **Aufnahmepfade ?**
dermal, inhalativ, oral
- **Wer ist exponiert ?**
Alle Verbraucher, Untergruppen

Kinetik

- Absorption
- Distribution
- Metabolismus
- Elimination


äußere Exposition
und
innere Exposition ?

Wieviel Fremdstoff (...) gelangt zu Zielstrukturen (...) ?

Cosmetic Ingredients* Opinions by the **SCCP / SCCS**

*** Preservatives, UV Filter, Fragrances, others**

- **Parabens (several)**
- **Triclosan**
- **ortho-Phenolphenol**
- **Benzophenones and derivatives**
- **Homosalate**
- **4-Methylbenzylidene-camphor**
- **3-Benzylidene camphor** →
- **Polycyclic musk fragrances**
- **Cyclosiloxanes (D4, D5)**
- **Melatonin** (in hair tonic)
- **Resorcinol**
- **Kojic acid**



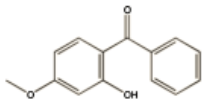
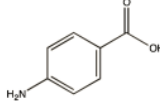
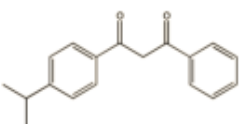
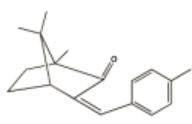
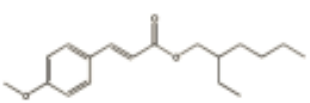
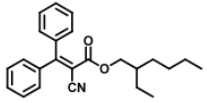
Endocrine activities and related effects evaluated in relation to exposure ...

↓

Safety/Risk assessment used for **Regulations:**

- a) on **permitted use levels** in cosmetic products or ..
- b) **restrictions / ban of an ingredient** when MOS < 100 or safe levels cannot be defined ...

UV-Filter: Some structures, examples

<p>Benzophenones</p> 	<p>Benzophenone-3</p>	<p>PABA <i>para</i>-amino-benzoic acid</p> 
<p>Dibenzoylmethanes</p> 	<p>Isopropyl-Dibenzoylmethanes (Eusolex 8020)</p>	<p>Camphor 4-methylbenzylidene camphor (Enzacamene)</p> 
<p>Cinnamates</p> 	<p>Ethylhexyl methoxycinnamate</p>	<p>Octocrylene (diphenylacrylat)</p> 

UV Filter

I

Table (modified) from: Krause M et al. (2012) *Sunscreens: are they beneficial for health? An overview of endocrine disrupting properties of UV filters*. *Int J Androl* 35: 424-436

Table 1 Most common UV-filters in cosmetics

	Generic name	Product name	Max concentration (%)	Spectrum of action
Chemical UV-filters	Benzophenone-3	BP-3	6 ^b -10 ^{a,c}	UV-A, UV-B
	2-Cyano-3,3-diphenyl acrylic acid	OCT	10	UV-B
	→ 3-Benzylidene camphor	3-BC	2	UV-B
	3-(4-Methyl-benzylidene) camphor	4-MBC	4	UV-B
	2-Ethylhexyl 4-methoxy cinnamate	OMC	7.5 ^b -10 ^{a,c}	UV-B
	Homosalate	HMS	10 ^a -15 ^{b,c}	UV-B
	2-Ethylhexyl 4-dimethylaminobenzoate	OD-PABA	8	UV-B
	4-Aminobenzoic acid	PABA	15 ^{b,c}	UV-B
Physical UV-filter	Titanium dioxide		25	Physical
	Zinc oxide		25-no limit	Physical

^aList of permitted UV-filters in the Council Directive of the European Committee.

^bList of permitted UV-filters in the US Food and Drug Administration monograph.

^cList of permitted UV-filters in the Australian regulatory guidelines for over-the-counter medicines (ARGOM), by the therapeutic Good Administration.

Full safety evaluations for UV Filters available at:

https://ec.europa.eu/health/scientific_committees/consumer_safety/opinions_en

UV Filter

II

- Axelstad M, Hass U, Kinnberg KL, Bjerregard P (2013) *Assessment of the endocrine disrupting potential of 23 UV filters*. Danish Centre of Endocrine Disruptors

Table 1. The evaluated UV-filters (INCI names)

BENZOPHENONE-4	DIETHYLAMINO HYDROXYBENZOYL HEXYL BENZOATE	ETHYLHEXYL TRIAZONE	PHENYLBENZIMIDAZOLE SULFONIC ACID
BENZOPHENONE-5	DIETHYLHEXYL BUTAMIDO TRIAZONE	HOMOSALATE	POLYACRYLAMIDOMETHYL BENZYLIDENE CAMPHOR
BENZYLIDENE CAMPHOR SULFONIC ACID	DISODIUM PHENYL DIBENZIMIDAZOLE TETRASULFONATE	ISOAMYL P-METHOXYCINNAMATE	POLYSILICONE-15
BIS-ETHYLHEXYLOXYPHENOL METHOXYPHENYL TRIAZINE	DROMETRIZOLE TRISILOXANE	METHYLENE BIS-BENZOTRIAZOLYL TETRAMETHYLBUTYLPHENOL	TEREPHTHALYLIDENE DICAMPHOR SULFONIC ACID
BUTYL METHOXYDIBENZOYL METHANE	ETHYLHEXYL DIMETHYL PABA	OCTOCRYLENE	TITANIUM DIOXIDE
CAMPHOR BENZALKONIUM METHOSULFATE	ETHYLHEXYL SALICYLATE	PEG-25 PABA	

Former review of data for 7 UV filters in another context:

- Hass U, Christiansen S, Axelstad M, Boberg J, Andersson AM et al. (2012) *Evaluation of 22 SIN List 2.0 substances according to the Danish criteria for endocrine disruptors*. Danish Centre of Endocrine Disruptors
Benzophenone-1, 2, and 3 (BP-1,2 and 3), 3-Benzylidene camphor (3-BC); 4,4'-Dihydroxybenzophenone; 4-Methylbenzylidene camphor (4-MBC); Ethylhexyl methoxycinnamate (OMC)

Short term testing: some examples

Receptor binding

- Blair RM, Fang H, Branham WS et al. (2000) The **estrogen receptor relative binding affinities of 188 natural and xenochemicals**: structural diversity of ligands. *Toxicol Sci* 54:138-153
- Fang H, Tong W, Branham WS et al. (2003) **Study of 202 natural, synthetic, and environmental chemicals for binding to the androgen receptor**. *Chem Res Toxicol* 16: 1338-1358

in vitro bioassays

- Byford JR, Shaw LE, Drew MGB et al. (2002) Oestrogenic activity of **parabens** in MCF-7 breast cancer cells. *J Steroid Biochem Molec Biol* 80: 49-60
- Schreuers RHMM, Sonneveld E, Janssen JHJ, Seinen W, van der Burg B (2005) Interaction of **polycyclic musks and UV filters** with the estrogen receptor (**ER**), androgen receptor (**AR**), and progesterone receptor (**PR**) in reporter gene bioassays. *Toxicol Sci* 83: 264-272
- Suzuki T, Kitamura S, Khota et al. (2005) **Estrogenic and antiandrogenic** activities of **17 benzophenone derivatives** used as UV stabilizers and sunscreens. *Toxicol Appl Pharmacol* 203: 9-17 **& → in vivo bioassays**
- Van Meeuwen JA, van Son O, Piersma AH et al. (2008) Aromatase inhibiting and combined estrogenic effects of **parabens** and estrogenic effects of **other additives in cosmetic products**. *Toxicol Appl Pharmacol* 230: 372-382

UV Filter

III

Key aspects in the safety evaluation:

- **Local effects?** **Systemic effects?**
- **Critical endpoint(s) → NO(A)EL ?**
- **Sufficient info/data on ... ??**
- **Human exposure scenario**

Notes of Guidance, latest version of 25 april 2016:
SCCS/1564/15

Checklists for Dossier submission: SCCS/1588/17

* * * * *

Evaluation of a new **organic UV Filter** with poor solubility and very low dermal penetration (< 1%):

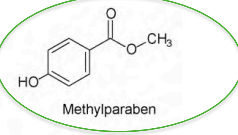
Scientific Committee of Consumer Safety (SCCS) Opinion on the safety of cosmetic ingredients **Phenylen Bis-Diphenyltriazine** (CAS No 55514-22-2) – **S86** – Submission II **SCCS/1594/18** (public consultation)

Low bioavailability (oral, dermal) !

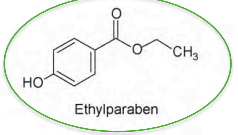


Systemic effects also highly unlikely to occur for inorganic UV Filter !

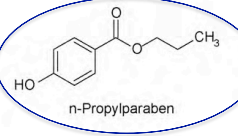
Parabens: Structures – Evaluations



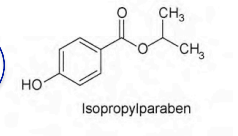
Methylparaben



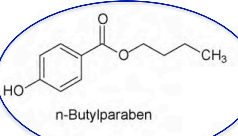
Ethylparaben



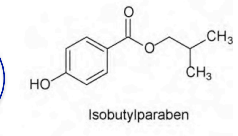
n-Propylparaben



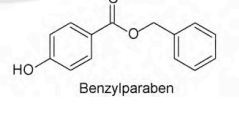
Isopropylparaben



n-Butylparaben



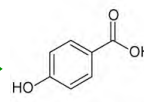
Isobutylparaben



Benzylparaben

Skin, Liver

→



Parahydroxy-benzoic acid

inactive Metabolite

SCCP/0873/05, SCCP/0874/05,
SCCP/1017/06, SCCP/1183/08,
SCCS/1348/10, SCCS/1446/11,
SCCS/1514/13

MeP, EtP safe at 0.4% & mix 0.8%
*BuP, PrP sum at 0.19% safe**

* Not to be used in leave-on products in the nappy area due to immature metabolism of infants < 6 months

Exposition (engl. Exposure) Parabene

'Default': **Konservierungsmittel** in **allen** Produkten (Menge: 17,4 g) bzw. Körperpflegeprodukten = 269 mg/kg KG/Tag (Erwachsene)

Paraben-Gehalte im Produkt (EU-Regulation):

Methyl-P / Ethyl-P je 0,4 % (0,8 %)	: 1,08 mg MeP / EtP per kg KG/Tag
Propyl-P / Butyl-P 0,19 %	: 0,51 mg PrP / BuP „ „

- **Womit ? Wie hoch ?**
Kosmetika, Nahrung, Pharmaka
- **Aufnahmepfade ?**
dermal, inhalativ, oral
- **Wer ist exponiert ?**
Erwachsene und (Klein-)Kinder

äußere Exposition !

- **Dermale Penetration**
- **Metabolismus**
- **Ausscheidung (HBM)**

innere Exposition ?

Related issues ...

Environmental Health Perspectives 123(5): A120 (2015)
FOCUS: Taking stock of personal care product safety

But **substitutions aren't simple**. For instance, consumers have recently been reporting **allergic reactions to a preservative called methylisothiazolinone (MI)**.¹² MI is not new, but **companies started relying on it more as they have turned away from parabens**. People apparently became sensitized to MI through increased exposure, and some ...

U.S. sales of “natural“ personal care products grew by an estimated 7.5% in 2014, faster than the personal care product market as a whole ...



Botanicals as cosmetic ingredients

Some examples

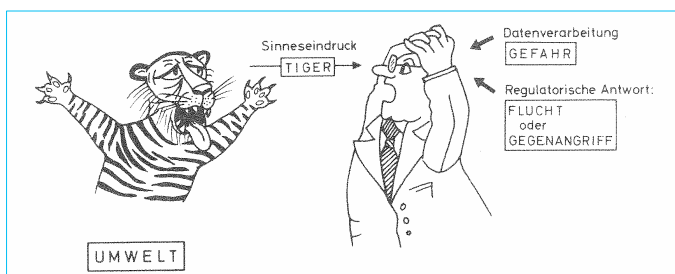
- β -Arbutin → SCCS/1552/15
- *Lawsonia inermis* (Henna) → SCCS/1511/13
- *Indigofera tinctoria* → SCCS/1439/11
- *Tea-tree oil* → SCCP/1155/08

Phyto-estrogens for topical application

- Lin JY et al. (2008) Topical **isoflavones** provide effective photo-protection to skin. *Photodermatol Photoimmunol Photomed* 24: 61–66
- Silva AP et al. (2009) Development of topical nanoemulsions containing the isoflavone **genistein**. *Pharmazie* 64(1):32-5.
- Iovine B et al. (2012) A comparative analysis of the photo-protective effects of **soy isoflavones** in their aglycone and glucoside forms. *Int J Mol Sci.* 13(12):16444-56.
-

Als Antioxidantien in Lichtschutzmitteln von Interesse !

Stress induced responses ...



Stress triggers
noradrenalin,
glucocorticoids,

...



Cartoon: Friedrich Marks – Molekulare Biologie der Hormone - UTB



Opinion

TRENDS in Molecular Medicine Vol.13 No.7

2007

Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health

Michael J. Meaney^{1,2}, Moshe Szyf^{1,3} and Jonathan R. Seckl⁴

Endokrin aktive Substanzen in Sonnenschutzmitteln

- ✧ **Endocrine Active Substance / Endocrine Disruptor**
 - Definitions; Concerns;
 - Modes of Action; Challenges
- ✧ **European Regulatory Arena** – diverse tasks
 - Criteria for identification of an Endocrine disruptor
- ✧ **SCCS (& others) on EAS/ED as Cosmetic Ingredients**
 - Safety evaluation: *Hazard, Exposure and Risk assessment*
 - UV filter: Annex VII compounds
 - Parabens: safe levels defined, but ... (*Science // other players*)

Apologies for d-english

Ausblick – Diskussion

Danke für Ihr Interesse !



LEIBNIZ RESEARCH CENTRE
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