Assessment of Reproductive Toxicity under REACH July 2012

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Position Paper

Aulmann (2012), Assessment of reproductive toxicity under REACH. Regul. Toxicol. Pharmacol. 63 (2012) 286-290

“Toxic to reproduction“

Subcategories GHS / CLP

Developmental toxicity / teratogenicity

- Malformations of progeny, functional defects, reduced growth, damaged organs, functional impairment (immune functions, behaviour)

Impairment of fertility

- Reduced sperm quality, disruption of hormone status, impairment of libido, sexual behaviour

Typology of tests

Test method / End point	**Developmental toxicity**	**Impairment of fertiliy**
OECD TG 421	Screening	Screening
OECD TG 422	Screening	Screening
OECD TG 407	(Not relevant)	Screening
OECD TG 416	(limited relevance)	Definitive test
OECD TG 414	Definitive test	Not relevant

Developmental Toxicity

OECD TG 414

Species:

- rats, rabbits

Protocol

- Treatment day 6 through 20 of gestation
- 3 dose groups, 1 control group
- Clinical observations during in-life phase
- Day 20 preparation of fetuses
- Visceral and skeletal analysis

Biologically significant parameters

- Maternal toxicity
- Embryo/ fetotoxicity
- Teratogenicity

Parameters for investigation

Maternal toxicity

- Body weight, water and food intake
- Clinical observations
- Necropsy

Embryo- Fetotoxicity

- Uterus- and plazenta weights
- Number of corpora lutea
- resorptions
- Number and weight of fetus
- Sex ratios / life lethal birth

Teratogenity

- Skeletal changes
- Visceral changes

Focus: potential harm to unborn child

Impairment of male / female fertility

OECD TG 415 / OECD 416

Species:

- Rats, mice

Protocol

- Treatment (7d/week)
  - males: over a full spermatogenesis-cycle
  - females: over 2 estrus-cycles und and during gestation and breeding
- Clinical observation
- Necropsy and histopathology

Biologically significant effect descriptors

- Reproductive integrity and performance (P / F1 (F2))

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Reproductive integrity and performance

Parameters for investigation in the OECD 415/416

- Gonads
- Estrous cyclus
- Mating behaviour
- Conception
- Birth
- Lactation

OECD 422 screening test *

Species:

- Rats

Protocol

- Treatment (7d/week)
  - Males: 4 w
  - Females: approx. 7 w
  - F1: 4 d
- Clinical observation
- Necropsy and histopathology

Biologically significant effect descriptors

- Repeated dose toxicity
- Reproductive performance

* OECD 421: similar approach but not combined with repeated dose toxicity

For differences see back-up slide

Historical background

Trigger

- Data gaps for many High-Production-Volume (HPV)- substances in terms of reprotox

Aim

- Identification of critical substances
- High through-put solution

What they are not aiming at

- Substitution of definitive studies (OECD 414/415/416)

OECD-Screening tests 421 / 422

A rough comparison

OECD 421/422

Investigations related to reprotox ± the same

OECD 422

+ Hematology, clinical chemistry, urinalysis
+ all organs: histopathology, organ weight

→ Information about repeated dose toxicity → ‚combined test‘

Conclusion: OECD 422 is given preference over OECD 421

OECD test 407

OECD 407 (28-day-study) is the conventional tier-1-method in Europe to investigate repeated dose toxicity of industrial chemicals

It was upgraded in 1995 to cover also reproductive parameters.

With respect to fertility the prediction value of the OECD 407 28 days study is comparable to the OECD 421/422

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Methods evaluation

421/422

407

Detection of detrimental effects on fertility

„Histology of male reproductive organs is more sensitive than conventional fertility parameters“ ([Ulbrich und Palmer,1995, Reuter et al, BUA, Mangelsdorff et al)

„Detailed histology is applicable also to investigate female fertility“ (Sanbuisho, et al.]

Detection of developmental toxicity

„insufficient“ [Reuter et al, 2003, BUA]

Out of scope

Animal numbers compared

OECD 414, 415, 416:

- 20 M, F

OECD 422:

- 10 M, F

OECD 407:

- 10 M, F

Reduced statistical resolution

- 1/10-Problem

Question of relevance of non significant effects

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Investigation of Reproductive Toxicity

REACH requirements for 10 – 100 ton (annex VIII):

Screening tests (OECD 421 or OECD 422)

- Pros:
  - Quick approach
  - Lower number of animals compared to definitive studies
- Cons:
  - Low statistical resolution
- No investigation of developmental effects (terata, malformations)

<u>However:</u>

Screening tests are mandatory under REACH!

No freedom of choice for higher tier (definitive) tests!

Higher tier testing requires prior time-consuming ECHA approval

REACH annex VIII data requirements

Current legislation (1) – mandatory without alternative

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REACH annex VIII data requirements

Current legislation (2) – mandatory

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REACH annex VIII data requirements

As an alternate approach (GT-AK-RegTox proposal)

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Proposal

414

407

Out of scope

Detection of detrimental effects on fertility

„Histology of male reproductive organs is more sensitive than conventional fertility parameters“ ([Ulbrich und Palmer,1995, Reuter et al, BUA, Mangelsdorff et al)

„Detailed histology is applicable also to investigate female fertility“ (Sanbuisho, et al.]

Detection of developmental toxicity

Literature


GDCh
Gesellschaft
Deutscher Chemiker
Beratergremium
für Altstoffe (BUA)
BUA-Bericht 229
(Februar 2001)
Evaluierung der OECD-Screening-Tests 421 (Reproduction/Developmental Toxicity Screening Test) und 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test)
S. Hirzel
Wissenschaftliche Verlagsgesellschaft

Literature

ACADEMIC PRESS

Available online at www.sciencedirect.com

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Regulatory Toxicology and Pharmacology 38 (2003) 17–26

Regulatory Toxicology and Pharmacology

www.elsevier.com/locate/yrtph

Evaluation of OECD screening tests 421 (reproduction/developmental toxicity screening test) and 422 (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test)

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Proposal 2012 *

[…]

Registrants should be allowed to select between these two options, either the existing approach (OECD TG 421/407 and alternatively TG 422) or the approach proposed in this paper (OECD TG 407 plus TG 414).

* „German Society of Toxicology, Committee for Regulatory Toxicology“

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Questions
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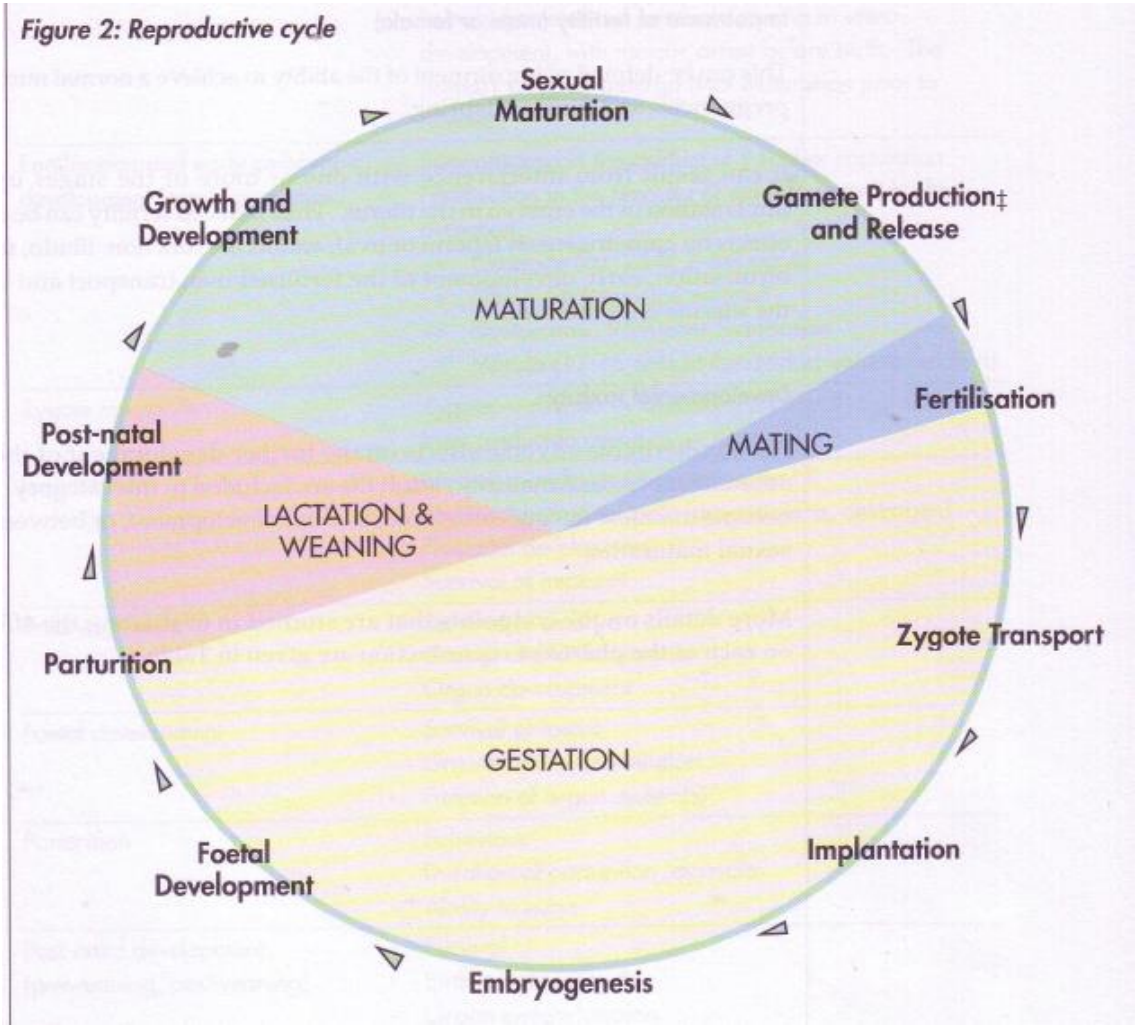
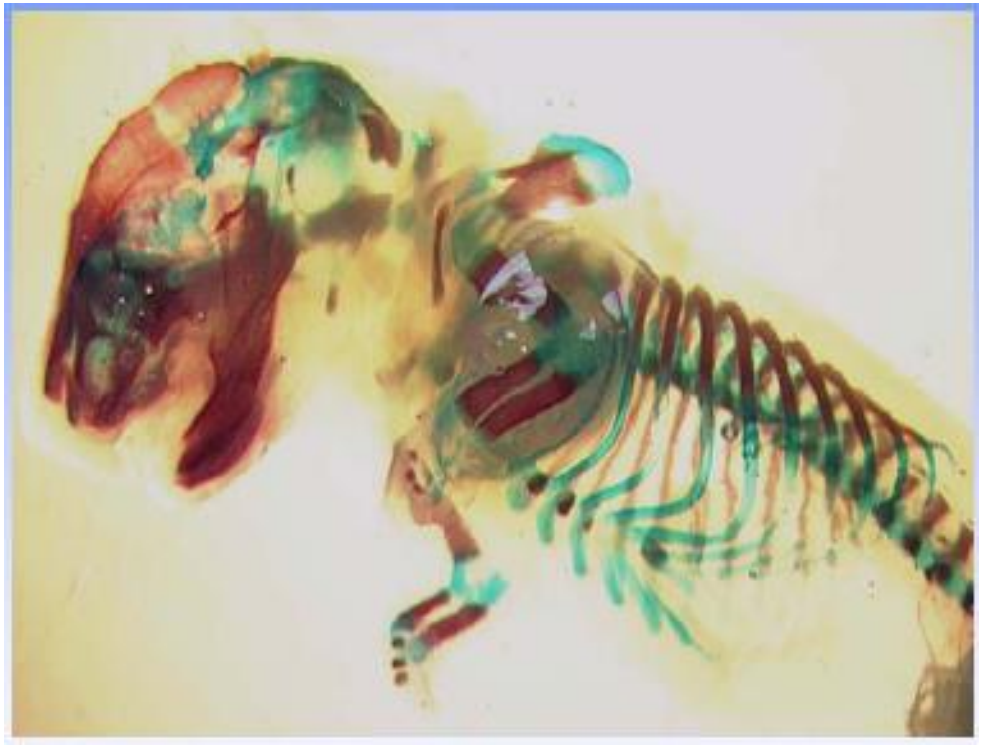
Reproduction Cycle

What we are talking about



Source: ECETOC Monograph No. 31

Illustration on skeletal investigations

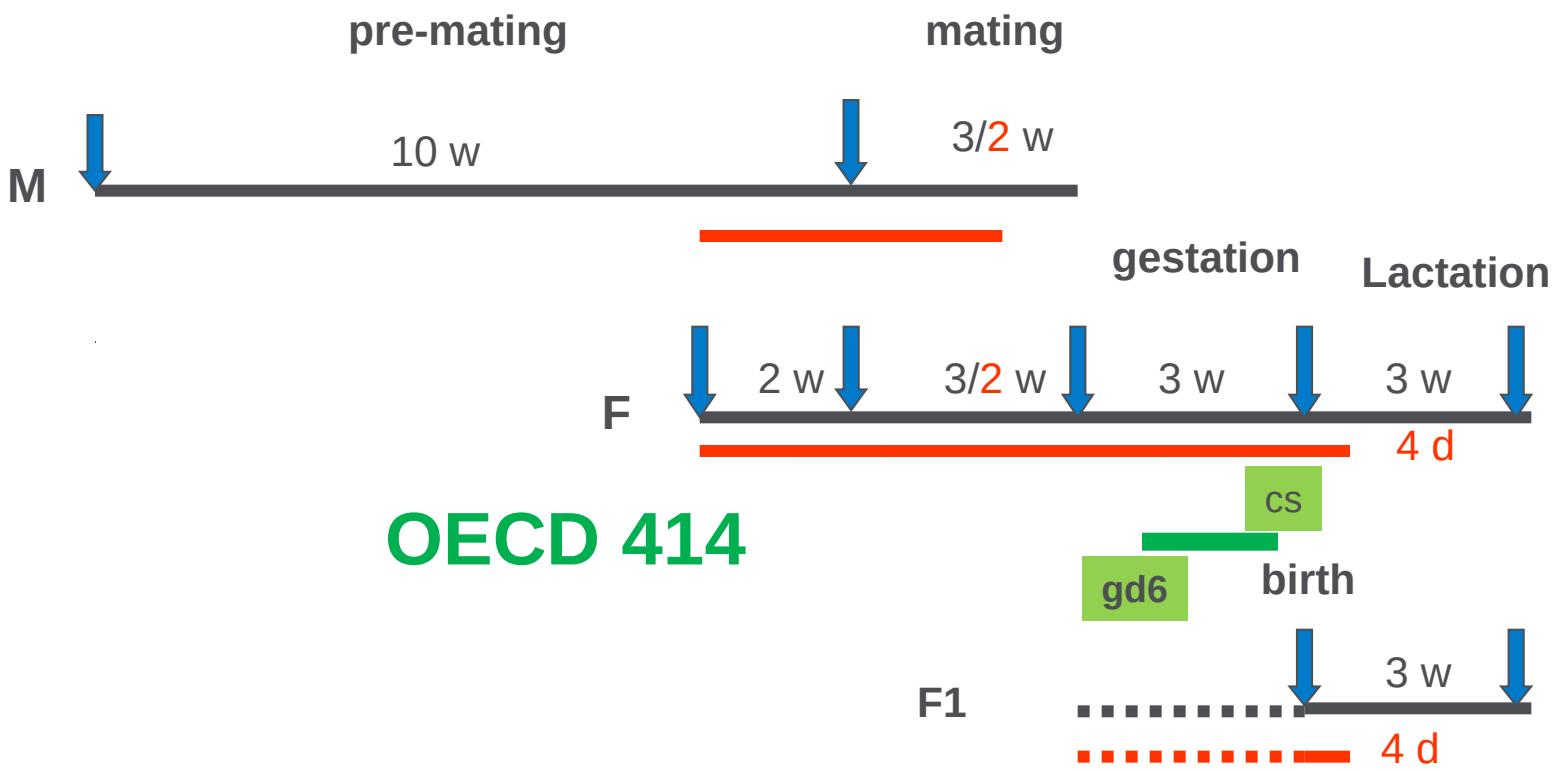


Rat fetus

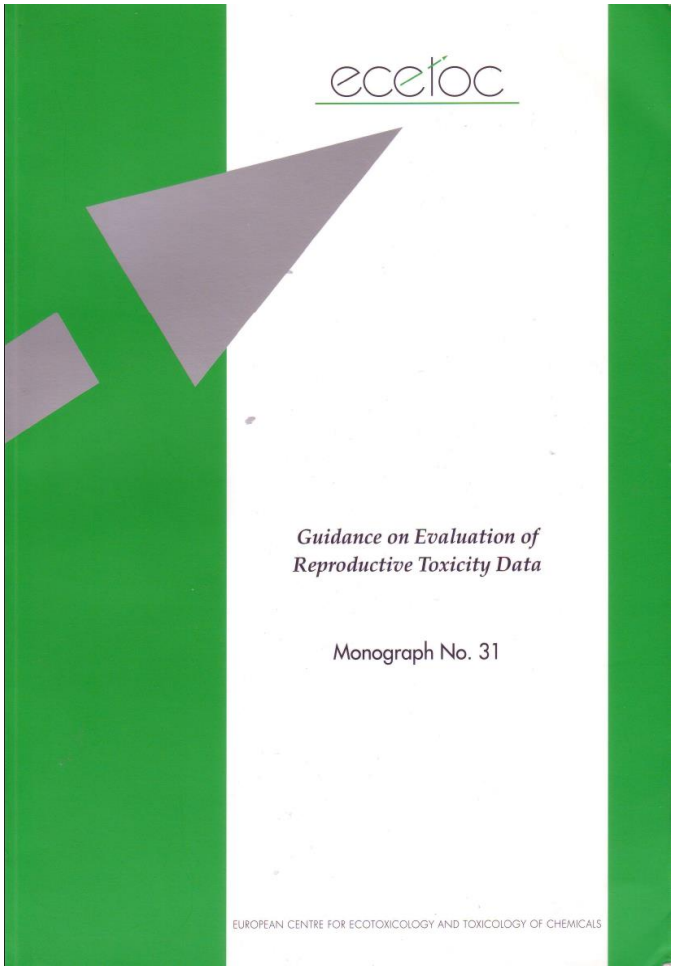
kindyl provided by J. Buschmann, ITEM, Fraunhofer, Hannover)

OECD tests 414 / 415 / 421/422

A comparison of study designs



Literature


ecetoc
Guidance on Evaluation of Reproductive Toxicity Data
Monograph No. 31
EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS