

Developmental neurotoxicity & REACH

Hannele Huuskonen

DNT WS 2016



REACH Article 1

- The purpose of this Regulation is to ensure a high level of protection of human health and the environment, including the promotion of alternative methods for assessment of hazard of substances, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation.



Information requirements for developmental neurotoxicity

- **REACH**

- Not a standard information requirement
- Based on a particular concern within an extended one-generation reproductive toxicity study
- Based on a particular concern under repeated dose toxicity?

- **C&L aspects**

- Information must be applicable also for C&L

Reproductive toxicity information requirements under REACH (cumulative)

- At 10 – 100 tonnage band (Annex VIII)
 - OECD TG 421 or 422
 - EU TM B.31/OECD TG 414 or **B.56/OECD TG 443** may be proposed
- At 100 – 1000 tonnage band (Annex IX)
 - EU TM B.31/OECD TG 414 (1st species; + 2nd species if triggered)
 - EU TM **B.56/OECD TG 443** if triggered (results from e.g. 28- , 90-day or screening study or other concern)
- Over 1000 tonnage (Annex X)
 - EU TM B.31/OECD TG 414 (1st + 2nd species)
 - EU TM **B.56/OECD TG 443**

EOGRTS design?

- **Aspects specified for REACH:**
 - Length of the pre-mating exposure duration
 - Starting point 10 weeks, can be shortened based on substance specific justifications
 - ECHA Guidance, reflecting Recital 7 of Regulation (EU) 2015/282
 - Highest dose level should be selected with the aim to produce some toxicity
 - ECHA Guidance, reflecting Recital 7 of Regulation (EU) 2015/282
 - Extension of Cohort 1B based on certain criteria (Column 2)
 - Inclusion of **DNT Cohorts 2A and 2B** based on triggers (Column 2)
 - Inclusion of Cohort 3 based on triggers (Column 2)

Relevant REACH processes

- **Dossier evaluation:** to fulfil **data gaps** for SIR and column 2 criteria for triggers
 - **Compliance check evaluation:** ECHA selects the registration dossier to be evaluated, requests a specific study design if missing
 - **Testing proposal evaluation:** The registrant proposes the study and the study design (following ECHA Guidance) if information not covered by an adaptation
- **Substance evaluation:** to request further data beyond the SIR based on **further concern**
 - MSCAs evaluates

Inclusion of DNT Cohorts 2A and 2B in an EOGRTS

- Need to be included if there is a **particular** concern on (developmental) neurotoxicity justified by any of the following:
 - existing information on the **substance itself** derived from relevant available *in vivo* or non-animal approaches, or
 - **specific mechanism/modes of action** of the substance with an association to (developmental) neurotoxicity, or
 - existing information on effects caused by **substances structurally analogous** to the substance being studied, suggesting such effects or mechanisms/modes of action

ECHA Guidance: **DNT Cohorts**, examples

- **Specific mechanisms/mode of action** that has been closely linked to (developmental) neurotoxicity effects
 - (Adult) brain cholinesterase inhibition (by 20%)
 - Relevant changes in **thyroid hormone levels** or signs of **thyroid toxicity** indicating such changes
 - Specific hormonal mechanisms/modes of action with clear association with the developing nervous system, such as **oestrogenicity** (Fryer *et al.*, 2012) and **anti-androgenicity** (Pallarés *et al.*, 2014)(organ weight changes/effects described in OECD GD 150 are used to identify these modes of actions)



Other options for DNT studies

- Column 2:
- *“Other studies on developmental neurotoxicity and/or developmental immunotoxicity instead of cohorts 2A/2B (developmental neurotoxicity) and/or cohort 3 (developmental immunotoxicity) of the Extended One-Generation Reproductive Toxicity Study **may be proposed** by the registrant in order to clarify the concern on developmental toxicity.”*
- To be considered if there is no concern for reproductive toxicity, only for DNT, or if a separate study can be justified (e.g., more/further parameters needed)

Use of non-animal approaches - General adaptations REACH

- Annex XI, Sections...
 - 1.1 Use of existing data
 - 1.2 Weight of evidence
 - 1.3 (Q)SAR
 - 1.4 *In vitro* methods
 - 1.5 Grouping of substances and read-across approach
 - 2 Testing is technically not possible
 - 3 Substance-tailored exposure-driven testing
- Data must be adequate for classification and labelling and risk assessment

Classification of DNT effects

- Data should allow adequate evaluation and classification categorisation + risk assessment – also if non-animal approaches are part of data
 - High confidence level is needed for decision on categorisation
- Depending on the study design/test, the effects may reflect neurotoxicity or developmental neurotoxicity
 - Classification for neurotoxicity or for developmental toxicity?
 - Classification and categorisation are risk management measures
 - Important because of different regulatory down stream consequences in other legislations
- If developmental origin can be concluded then classification for developmental toxicity
- No experience yet

Classification categorisation for neurotoxicity

- Specific target organ toxicity (STOT)
- Single exposure:
 - **STOT-SE Category 1**
 - **STOT-SE Category 2**
- Repeated dose toxicity
 - **STOT-RE Category 1**
 - **STOT-RE Category 2**
 - **STOT-RE Category 3**
- No classification

STOT-SE/RE Category 1

- Substances that have produced **significant** toxicity in **humans** or that, on the basis of evidence from studies in experimental animals, can be **presumed** to have the potential to produce significant toxicity in humans following single/repeated exposure
- Substances are classified in Category 1 for specific target organ toxicity (single/repeated exposure) on the basis of:
 - (a) reliable and good quality evidence from **human** cases or epidemiological studies; or
 - (b) observations from appropriate studies in **experimental animals** in which **significant and/or severe** toxic effects of relevance to human health were produced at generally **low exposure** concentrations. Guidance dose/concentration values are provided below ... to be used as part of weight-of-evidence evaluation.

STOT-SE/RE Category 2

- Substances that, on the basis of evidence from studies in experimental animals can be **presumed** to have the potential to be **harmful** to human health following single/repeated exposure
 - Substances are classified in Category 2 for specific target organ toxicity (single/repeated exposure) on the basis of observations from appropriate studies in experimental animals in which **significant toxic effects**, of relevance to human health, were produced at generally **moderate exposure concentrations**. Guidance dose/concentration values are provided below ... in order to help in classification.
- In exceptional cases, human evidence can also be used to place a substance in Category 2.

STOT RE 1/2

- **Significant toxic effects** in a 90-day repeated-dose study conducted in experimental animals are seen to occur at or below the guidance values:

Route	Species	Units	RE 1 Dose/ concentration	RE 2 Dose/ concentration
Oral	(rat)	mg/kg bw/day	$C \leq 10$	$10 < C \leq 100$
Dermal	(rat or rabbit)	mg/kg bw/day	$C \leq 20$	$20 < C \leq 200$
Inhalation (gas)	(rat)	ppmV/6h/day	$C \leq 50$	$50 < C \leq 250$
Inhalation (vapour)	(rat)	mg/litre/6h/ day	$C \leq 0.2$	$0.2 < C \leq 1.0$
Inhalation (dust/mist/ fume)	(rat)	mg/litre/6h/ day	$C \leq 0.02$	$0.02 < C \leq 0.2$

Classification categorisation, developmental toxicity

- Regarding to reproductive toxicity (including **developmental toxicity**) the categorisation is as follows:
 - **Repr 1A**: mainly based on information on humans
 - **Repr 1B**: mainly based on information on animal studies, findings considered relevant to humans, not secondary to other toxicity and severe and/or high incidence [= clear evidence]
 - **Repr 2**: findings that do not warrant categorisation to Repr 1B [=some evidence]
 - **No** classification
- Reproductive toxicity includes according to CLP:
 - adverse effects on **sexual function and fertility** in adult males and females
 - **developmental toxicity** in the offspring

Adverse effects on development of the offspring

- Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, **developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure**. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) **functional deficiency**.

Test methods in REACH

- Test methods shall be regularly reviewed and improved... (REACH Art 13(2))
- While the classification of any substance or mixture may be carried out on the basis of available information, the available information to be used for the purposes of this Regulation should preferably have been generated **in accordance with the test methods referred to in Regulation (EC) No 1907/2006**, transport provisions or international principles or procedures for the validation of information, so as to ensure quality and comparability of the results and consistency with other requirements at international or Community level. The same test methods, provisions, principles and procedures should be followed where the manufacturer, importer or downstream user chooses to generate new information. (CLP Recital 21)

Assessment and validation of alternative test methods

The test methods in Commission Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) are **regularly reviewed and improved with a view to reducing testing on vertebrate animals and the number of animals involved**. The European Centre for the Validation of Alternative Methods (ECVAM) of the Commission's Joint Research Centre plays an important role in the scientific **assessment and validation of alternative test methods**. (CLP Recital 26)

Non-animal approaches

- Information on intrinsic properties of substances may be generated by means other than tests, provided that the **conditions set out in Annex XI are met**. In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods,... (REACH Art 13(1))
- The generation of information by alternative means offering **equivalence** to prescribed tests and test methods should also be allowed, ...(REACH Recital 38)
- Where new tests are carried out for the purposes of this Regulation, tests on animals within the meaning of Directive 86/609/EEC shall be undertaken only **where no other alternatives, which provide adequate reliability and quality of data, are possible**.(CLP Art 7)

GLP and other international standards

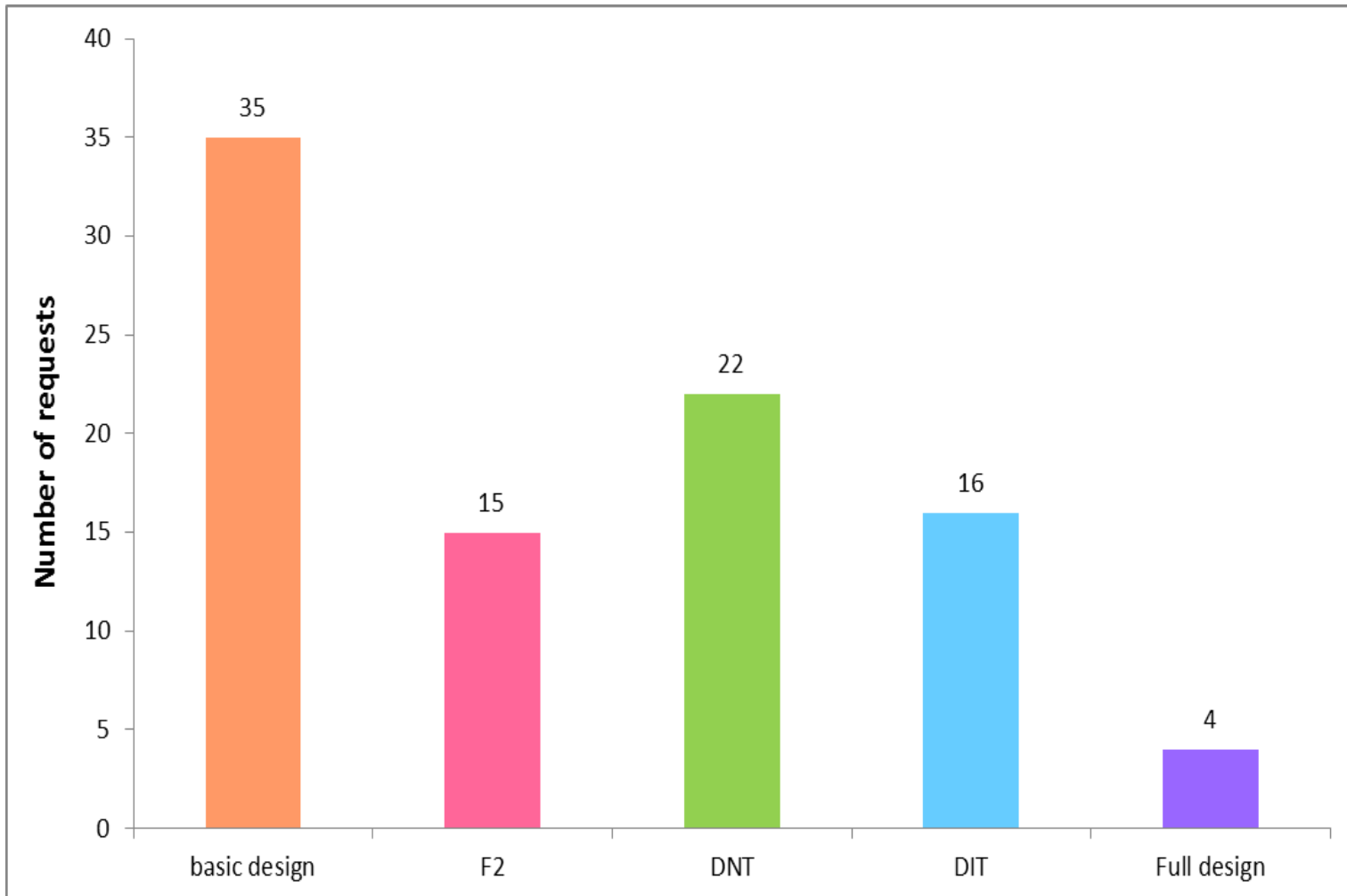
- ... and toxicological tests and analysis shall be carried out in compliance with the principles of good laboratory practise... and other international standards recognised as being equivalent by Commission or the Agency... (REACH Art 13(4))
- Where the manufacturer, importer or downstream user carries out new ecotoxicological or toxicological tests and analyses, these shall be carried out in compliance with Article 13(4) of Regulation (EC) No 1907/2006. (CLP Art 8)

Regarding to biological availability...

Specific cases requiring further evaluation

- (b) conclusive scientific experimental data show that the substance or mixture is **not biologically available** and those data have been ascertained to be **adequate and reliable** (CLP Art 12)
- Testing ... may be omitted where justified by information on exposure and implemented risk management measures as specified in Annex XI, section 3 (REACH Art 13(1))

Study expansions of EOGRTS in draft decisions (distribution may change in final decisions)



Summary (1)

- Under **REACH** Regulation DNT can be required based on justified concern within an EOGRTS (under DEv and SEv)
 - DNT is an adaptation (column 2 requirement)
- OECD TG 426 or other studies/tests may be required under SEv
- Registrants may provide OECD TG 426 or other DNT studies instead of EOGRTS DNT Cohorts
- Registrants may provide information from non-animal (alternative) approaches as general adaptations according to Annex XI
 - Equivalent information

Summary (2)

- Available data should allow risk assessment (DNEL derivation) and classification and labelling, including categorisation
- Available data should allows adequate evaluation of data and classification categorisation between categories 1, 2 and no classification
- Classification for neurotoxicity (STOT-SE/RE 1 or 2) or developmental toxicity (Repr 1B) have significantly different downstream consequences

Thank You.

Hannele.huuskonen@echa.europa.eu

Subscribe to our news at echa.europa.eu/subscribe

Follow us on Twitter
[@EU_ECHA](https://twitter.com/EU_ECHA)

Follow us on Facebook
[Facebook.com/EUECHA](https://facebook.com/EUECHA)