

# Regulatory consideration in EU

**European stakeholders'  
workshop on new approach  
methodologies (NAMs) for  
developmental neurotoxicity  
(DNT) and their use in the  
regulatory risk assessment of  
chemicals**

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# Content of the presentation

- Current information requirements on DNT under REACH Regulation and Biocidal Products Regulation (BPR)
- Current CLP criteria for developmental toxicity
- ECHA perspectives of potential uses in hazard and risk assessment

# **Current information requirements under REACH Regulation**



## **DNT data required only at $\geq 100$ tonnes if particular concerns identified**

- Annex VII (one tonne or more) and VIII (10 tonnes or more): No DNT data required
- Annex IX (100 tonnes or more) and X (1000 tonnes or more): An EOGRTS including cohorts 2A/2B **in case of particular concerns on** (D)NT justified by:
  - existing information on the substance from relevant available in vivo or non-animal approaches (e.g. abnormalities of the CNS, evidence of adverse effects on the nervous system in studies on adult animals or animals exposed prenatally), or
  - specific mechanisms/modes of action of the substance with an association to (D)NT (e.g. cholinesterase inhibition or relevant changes in thyroidal hormone levels associated to adverse effects), or
  - existing information on effects caused by structurally analogous substances, suggesting such effects or mechanisms/modes of action.

Other studies on developmental neurotoxicity instead of cohorts 2A/2B of the EOGRTS may be proposed by the registrant in order to clarify the concern on developmental toxicity.

# Standard data requirements at $\geq 100$ tonnes that may identify “particular concerns on (developmental) neurotoxicity”

- skin corrosion and irritation in vitro and/or in vivo studies
- serious eye damage/eye irritation in vitro and/or in vivo study
- skin sensitisation in vitro/in chemico and/or in vivo study
- in vitro mutagenicity studies, in vivo mutagenicity studies (if triggered)
- acute oral, dermal and inhalation toxicity study
- 28-day study
- 90-day study
- screening study for reproductive/developmental toxicity (OECD TG 421 or 422)
- OECD TG 414 study in rats and/or rabbits

Annex XI allows adaptation from the standard requirements, where it can be justified and provide an **equivalent in level of information and suitability for risk assessment and classification and labelling.**

# Potential triggers for EOGRTS with cohort 2A and 2B among REACH data requirements

- Thyroid hormone (T4 and TSH) levels measured in blood in most of the studies (in OECD TG 407 only if an indication of effect), T3 also in OECD TG 408, 407 and 414.
- Thyroid weight and histopathology in most of the studies (in OECD TG 421 “may be examined when necessary”; in OECD TG 407 thyroid weight optional).
- Brain weight required only in OECD TG 422 and OECD TG 407 but only from adult animals.
- Histopathology of “representative regions” of cerebrum, cerebellum and pons”, spinal cord and peripheral nerve (sciatic or tibial) in most of the studies but only in adult animals (not in OECD TG 421 or OECD TG 414).
- Only in OECD TG 414 in rabbits, brain of foetuses is investigated for “soft tissue alterations”.
- All in vivo studies: general clinical observations (e.g. behavioral signs suggesting CNS depression (e.g. narcosis), abnormal gait, seizures) – sometimes difficult to differentiate from general toxicity.

**In conclusion, only limited endpoints currently investigated to identify particular concerns on (D)NT to trigger EOGRTS with DNT cohorts.**

## Other/additional data possibly provided by the REACH registrants

- REACH Annex VI: The registrant **should** collect all other available and relevant information on the substance regardless whether testing for a given endpoint is required or not at the specific tonnage level. This should include information from alternative sources (e.g. from (Q)SARs, read-across from other substances, in vivo and in vitro testing, epidemiological data) which may assist in identifying the presence or absence of hazardous properties of the substance and which can in certain cases replace the results of animal tests. New tests on vertebrates shall only be conducted or proposed as a last resort when all other data sources have been exhausted.
- CLP Art. 5: Manufacturers, importers and downstream users have always the **obligation** to identify and examine available information on substances and assess whether it is adequate, reliable and scientifically valid for the purpose of the evaluation of hazard information and decision on classification.

- There is no possibility under REACH to request DNT IVB as a standard data requirement (without legal change).
- If other data than those defined by Annex VII-X as the standard information requirements are provided by the registrant, ECHA will consider adequacy of such information and the acceptability against REACH adaptation rules (equivalent information, adequate for risk assessment, C&L, and identification for SVHC according to Art 57(f)).
- Under SEV (substance evaluation), in principle, the MSCAs can request any type of studies they consider relevant for safe use of the substance and the request can be justified with expected regulatory need. However, SEV covers only a limited number of substances.
- There is no possibility for ECHA to conduct itself, or to request the registrants to conduct DNT IVB (or any other tests outside standard information requirements) for prioritisation purposes.



**Current information  
requirements on DNT  
under Biocidal Products  
Regulation (BPR)**



# Information requirements for DNT in BPR

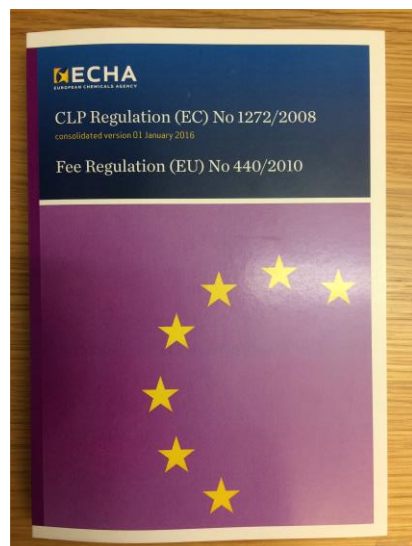
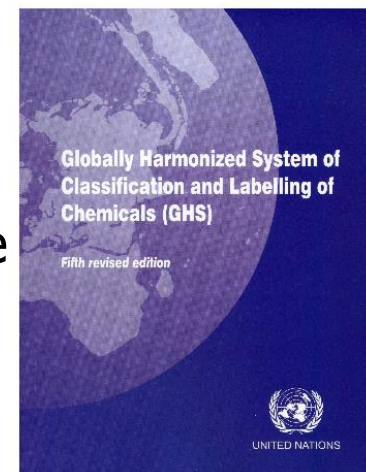
- Developmental Neurotoxicity Study in accordance with OECD TG 426, or any relevant study (set) providing equivalent information, or cohorts 2A and 2B of an Extended One-Generation Reproductive Toxicity study (OECD TG 443) with additional investigation for cognitive functions.
- DNT IVB does not provide equivalent information.
- The study shall not be conducted if the available data indicate that the substance causes developmental toxicity and meets the criteria to be classified as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and are adequate to support a robust risk assessment.

# **Current CLP criteria for developmental toxicity**



# Legal framework for classification and labelling in the EU - CLP Regulation

- Harmonised criteria for C&L carefully developed over 12 years, adopted within the United Nations structure  
⇒ the Globally Harmonised System of Classification and Labelling of Chemicals (GHS).
- CLP is based on GHS and implements GHS within the EU.



31.12.2008	EN	Official Journal of the European Union	L 353/1
<b>REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL</b>			
<b>of 16 December 2008</b>			
<b>on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006</b>			
<b>(Text with EEA relevance)</b>			
THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,			
Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,			
Having regard to the proposal from the Commission,			
Having regard to the opinion of the European Economic and Social Committee <sup>(1)</sup> ,			
Acting in accordance with the procedure laid down in Article 251 of the Treaty <sup>(2)</sup> ,			

## Hazard classification

- Aims to identify hazardous properties of chemicals.
  - Information about the **intrinsic properties** of a substance or mixture is evaluated by applying the criteria for classification in order to determine its potential to cause harm.
  - Should not be confused with risk assessment.
- ➡ Does not take exposure into consideration.

$$\boxed{\text{hazard}} \times \text{exposure} = \text{risk (GHS 1.1.2.6.2.1)}$$

# CLP central in protection against toxic chemicals in EU

- Provided that appropriate data is available and allows a proper conclusion on hazard class and category.
- CLP not a tool to generate data, but the available data should be used.
- In total about 20 EU legislations relate to CLP for triggering **risk management measures**
  - Depend on hazard class and category.
  - E.g. Active substances in BP or PPP with Repr. 1 (but not 2) (among certain other classifications/properties) shall not be approved unless certain conditions are fulfilled; CMR 1 (but not 2) can trigger restriction in consumer uses for a substance on its own, in a mixture or in an article (REACH Article 68 (2)).
- Different reasons for no classification:
  - lack of data
  - inconclusive data, or
  - data conclusive but not sufficient for classification

# Adverse effects on development of the offspring

(CLP Annex I, 3.7.1.4)

- In its widest sense any effect interfering with normal development of the conceptus, before or after birth, 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. These effects can be manifested at any time point in the life span.
- Major manifestations:
  - **death of the developing organism**
  - **structural abnormality**
  - **altered growth**
  - **functional deficiency.**
- Primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity.

# **Basis of classification for reproductive toxicity**

(CLP Annex I, 3.7.2.2)

- Assessment of the total weight of evidence in order to make a comparison with the criteria.
- Intended to be used for substances which have an intrinsic, specific property to produce an adverse effect on reproduction.
- In the evaluation of toxic effects on the developing offspring, important to consider the possible influence of maternal toxicity.
- No classification if reproductive toxicity is produced solely as a non-specific secondary consequence of other toxic effects.
- Reproductive toxicants are allocated to one of two categories: Category 1 (1A or 1B) or 2.
- Within each category, effects on sexual function and fertility, and on development, are considered separately.



## Reproductive toxicity Cat. 1: known or presumed human reproductive toxicant (CLP Annex I, Table 3.7.1(a))

- **Category 1A: Known** human reproductive toxicant
  - Largely based on **evidence from humans**.
- **Category 1B: Presumed** human reproductive toxicant
  - Largely based on **data from animal studies**.
  - Such data shall provide **clear evidence** of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects.
  - When there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

## **Reproductive toxicity Cat. 2: suspected human reproductive toxicant** (CLP Annex I, Table 3.7.1(a))

- **Some evidence** from **humans or experimental animals, possibly supplemented with other information**, of an adverse effect on sexual function and fertility, or on development.
- Where the evidence is not sufficiently convincing to place the substance in Category 1.
- If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification.
- Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

- All available information that bears on the determination of reproductive toxicity are considered together, e.g.:
  - epidemiological studies and case reports in humans
  - animal studies
  - data on chemically related substances, particularly when information on the substance is scarce
  - mechanism or MoA study results may provide relevant information which reduces or increases concerns about the hazard to human health
- A single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification.
- The weight given influenced by e.g.:
  - quality of the studies
  - consistency of results
  - nature and severity of effects
  - the presence of maternal toxicity in experimental animal studies
  - level of statistical significance for inter-group differences
  - number of endpoints affected
  - relevance of route of administration to humans
  - freedom from bias

## **In vitro assays, structure-activity relationships (SAR)** (CLP Annex I, 3.7.2.5.4.)

*"Evidence from in vitro assays, or non-mammalian tests, and from analogous substances using structure-activity relationship (SAR), can contribute to the procedure for classification. In all cases of this nature, expert judgement must be used to assess the adequacy of the data. Inadequate data shall not be used as a primary support for classification."*

## Is there a limit dose in the CLP criteria above which no classification is justified? (CLP Annex I, 3.7.2.5.7-9)

- **Not included** in the CLP criteria for reproductive toxicity
- Adverse effects on reproduction *only at very high dose levels* in animal studies (e.g. that induce prostration, severe inappetence, excessive mortality) would not normally lead to classification unless indications that humans may be more susceptible.
- A “limit dose” of 1000 mg/kg bw/day (oral) is specified in some OECD test guidelines
  - Applies only when human exposure does not indicate the need for a higher dose level to be used.

# Potency and classification for reproductive toxicity

- Potency is *not* stated in the CLP criteria for distinguishing between different hazard categories for reproductive toxicants (1A, 1B or 2).
- Potency is considered for setting specific concentration limit (SCLs) for a substance.
- Mixtures are classified for reproductive toxicity if they contain reproductive toxic substances at or above SCL or a generic concentration limit given in CLP (0.3% for Cat. 1A/1B and 3% for Cat. 2 substances).

# **Potential uses of DNT IVB in hazard and risk assessment**



## Potential uses of DNT IVB today

- Such data would be available for ECHA only if **voluntarily** performed and provided by IND to ECHA processes (no current standard information requirement under REACH, BPR).
- If provided by IND to relevant processes could be used in:
  - WoE in classification and labelling for developmental toxicity as supplemental information to animal/human evidence on the substance or another substance if read across justified.
  - triggering for further DNT tests at Annex IX and X: could supplement the data requirements under REACH
  - to support grouping and read across from similar substances already having positive animal/human evidence on DNT to propose risk management measures for the group where appropriate
  - to support prioritisation of authorities work (e.g. prioritising substances for further work with a view towards risk management).



# For the future: Chemical strategy for sustainability

- Aims at “PROTECTION AGAINST MOST HARMFUL CHEMICALS”
- CLP Regulation the central for hazard classification
  - *Commission to assess the need for specific criteria for immunotoxicity and neurotoxicity, currently under the hazard endpoints ‘Specific target organ toxicity’ and ‘reproductive toxicity’, and amend them if necessary.*
  - There will likely be developments including neurotoxicity.

# For the future: roadmap to more comprehensive information on DNT properties?

- Negative in vitro results do not exclude DNT properties (e.g. limited in vivo components as well as spatial and temporal aspects represented), however positive results useful especially where there is a lack of data currently.
- Also different in vivo protocols provide different levels of information. EOGRTS DNT cohorts lack cognitive parameters (e.g. associative learning and memory), included in OECD TG 426 (the most comprehensive available OECD TG for DNT).
- If the in vitro test protocols would be broadly accepted as ready for use as standard data requirements, could be used in triggering for further DNT tests via REACH Annexes. The current standard data requirements include only studies performed in accordance with validated and approved OECD TGs.
- To be used as the only data obligating to classify for developmental toxicity, a change in CLP and GHS would be needed.
- To be used as the only data in risk assessment, the data should be able to provide a point of departure (NOAEL and LOAEL).

# Thank you!

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