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Development of a rationale for a risk-based approach to Applications for Authorisation for OPnEO

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REASONS FOR PNEC DERIVATION FOR OPNEO

- Inclusion of OPnEO in REACH Annex XIV (June 14th, 2017) based on the critical degradation product 4-tert-octylphenol (4-t-OP)
- Application for Authorisation (AfA): Threshold identifiable?

  → PNEC (yes/no?) basis for decision making

"SEA" route? "Adequate control" route?

- No official reference concentration or concentration-response relationship available

  ⇨ Applicants' responsibility to assess the risks of using OPnEO, including a robust hazard assessment for the identified endocrine disrupting properties

DO THRESHOLDS EXIST FOR ENDOCRINE DISRUPTING SUBSTANCES?

- Conclusion from the SETAC Pellston Workshop (2016)[1]:

  Environmental risk assessments (ERA) for EDCs is "*scientifically sound and sufficiently reliable and protective of the environment*"

- Prerequisite: adequate characterisation of

  → Environmental exposure

  → Effects on relevant taxa

  → Influence on sensitive life stages

  → Delayed effects

  → Dose-/concentration response incl. consideration of NMDR

[1] http://onlinelibrary.wiley.com/doi/10.1002/ieam.1885/full

OVERALL PRACTICAL APPROACH

- **Step 1:** Data gathering for 4-t-OP (worst case assumption)

  → Review of “background documents”

  → Identification of new literature

- **Step 2:** Review of available information

  → Reliability (Klimisch scores)?

  → Relevance?

OVERALL PRACTICAL APPROACH

Step 3: Assignment of data to OECD levels 1 to 5

- OECD level 1: Existing data and non-test information
- OECD level 2: *In vitro* assays (selected endocrine mechanism pathways)
- OECD level 3: *In vivo* assays (selected endocrine mechanism pathways)
- OECD level 4: *In vivo* assays covering endocrine relevant endpoints
- OECD level 5: *In vivo* assays with more comprehensive data on endocrine endpoints

→ OECD level 4 & 5 data: Adverse effects on apical endpoints on individual and/or population level, considered relevant for hazard/risk assessment and suitable for PNEC derivation

→ OECD level (2 &) 3 data: mechanistic information, relevant for AOP

GENERAL OVERVIEW OF DATA – OECD LEVEL 3

- Taxonomic groups:
  - → Fish (marine & freshwater)
  - → Invertebrates
  - → Amphibians
- Effects information available:
  - → Biomarker/gene expression level, e.g. VTG in fish
  - → Apical endpoints partially investigated in OECD level 3 studies, e.g. fertility, reproduction and development

    However: Screening level data only, low precision of resulting NOEC/EC_x values!

GENERAL OVERVIEW OF DATA – OECD LEVEL 4

Table 1: Most sensitive endpoints affected in OECD level 4 studies

Taxonomic group	Indication of hormonal activity	Apical endpoint
Fish (marine & freshwater)	VTG induction Testis-ova	Weight and body length Sex ratio
Invertebrates	/	Larval malformations Embryo numbers
Amphibians	Serum T4 levels; Oestradiol and testosterone serum concentration	Growth Timing of metamorphosis Sexual development

GENERAL OVERVIEW OF DATA – OECD LEVEL 5

- Taxonomic groups:
  - → Fish (freshwater)
  - → Invertebrates
- Effects information available:
  - → Biomarker and other indication of hormone activity: VTG and testis-ova
  - → Reproductive parameters (e.g. fertility, number of eggs in fish; fecundity in invertebrates)

CONSIDERATION OF ADVERSE OUTCOME PATHWAYS (AOP)

- Linking the basic endocrine activity & molecular mechanism to adverse effects on the whole organism
- Comprises:
  - → Molecular initiating events (MIE), e.g. receptor binding
  - → MIEs lead to key events (KE), e.g. cellular change
  - → MIE (e.g. VTG induction) & KE (e.g. testis-ova) causally linked to adverse outcome (e.g. infertility)
- Aim of AOP: Reduce uncertainties in decision-making

NON-MONOTONIC DOSE-RESPONSE (NMDR)

- Evidence for NMDR for 4-t-OP?
- One single study indicates U-shaped NMDR in fish

  → VTG induction only

  → Finding not confirmed by any other fish studies employing the same concentration range

- Other cases of NMDR are reported, but always *inverted* U-shaped dose-response

  → Very unlikely that low-dose effects are missed

DERIVATION OF PREDICTED NO EFFECT CONCENTRATION (PNEC)

- Point of departure:
    i. NOEC of the most sensitive species and endpoint
    ii. HC5 from a species sensitivity distribution (SSD)

- Determination of appropriate assessment factors (AF), REACH guidance R.10:
    i. AF of 10 for long-term results from at least 3 species
    ii. AF 1–5 for SSD

THANK YOU

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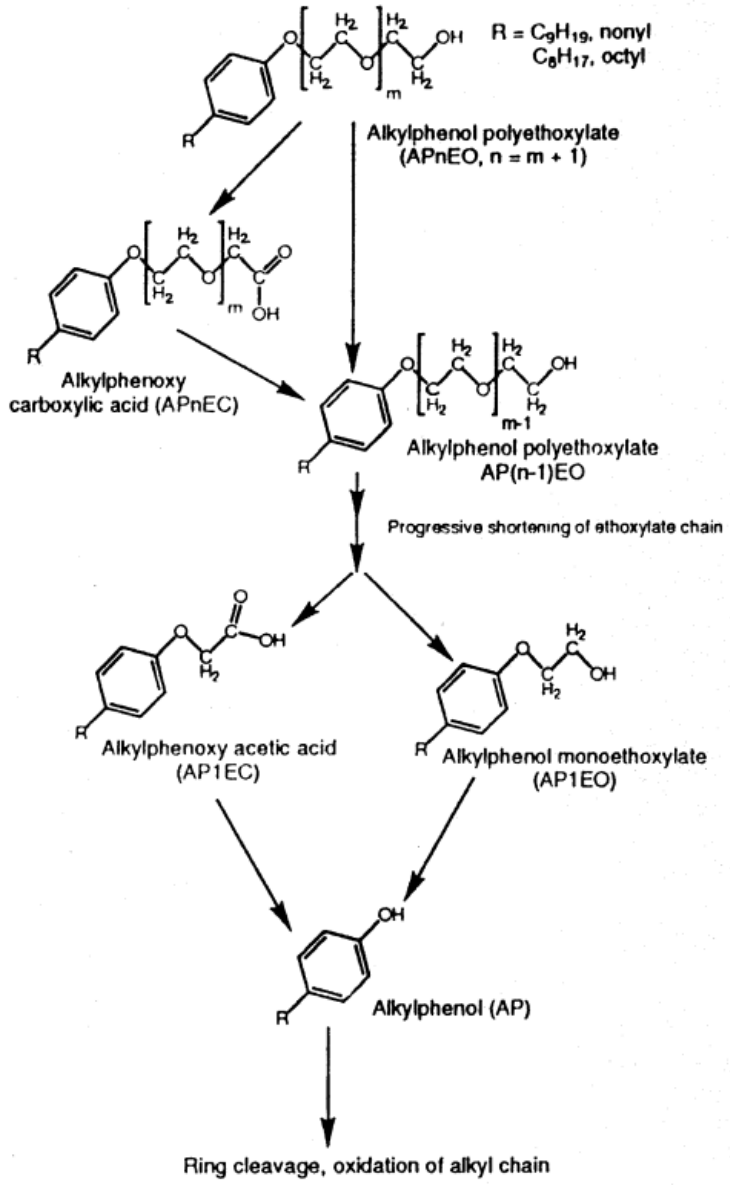
BIODEGRADATION SCHEME FOR ALKYLPHENOL ETHOXYLATES



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