The new guidance on Environmental risk assessment of feed additives

Parma, 20/11/2019

INDEX

Point of discussion

- Background
- Phase I: different steps
- Phase II: Environmental Risk Assessment
  - Phase II A – different steps & examples
  - Phase II B – different steps & examples
  - Phase II C – different steps & examples
- New EXCEL tool for calculation

BACKGROUND

Mandate: "The guidance on environmental risk assessment should be completely revised in order to take into account of new developments in methodology and the extensive documentation produced by EFSA Scientific Committee and other bodies (EMA, OECD)."

BACKGROUND

FEEDAP Guidance ERA feed additives 2008

- Based in two phases (I and II)
- When specific thresholds are reached in terrestrial or aquatic compartments in phase I, a phase II ERA assessment is needed.
- Harmonised with the CVMP/VICH (2005) Guideline for the terrestrial compartment
- In line with REACH Guideline for the aquatic compartment

BACKGROUND

NEW GUIDANCE

- Harmonisation within EFSA (e.g. pesticides, Scientific Committee new guidance)
- Harmonisation with other assessment bodies like EMA and ECHA (a contact has been established with EMA/CVMP)
- New developments in the field
- The experiences gained in the past years (2008 up to now)
- Characteristics: **practical** (to help in solving problems), **short**, **simple** (as much has been possible), covering uncertainties (as much as possible), cross refers to internal/external documents (EFSA, CVMP) or appendices

BACKGROUND

DISCUSSION GROUP

In compliance with the EFSA's Stakeholder Engagement Approach

- A call was sent to Consumers, Environmental/health NGOs and advocacy groups, Farmers and primary producers, Business and food industry, Practitioners' associations, Academia and Member States
- Business and feed industry organisations (6) and Association of practitioners (1) proposed 10 candidates
- 3 of Business and feed industry organisations were selected. They could comment the draft guidance at different stages of development.

BACKGROUND

PUBLIC CONSULTATION ON THE ERA GUIDANCE

From 8 Oct to 19 Nov 2018

EFSA received 133 comments from 11 interested parties

- 6 public organisations, (Spanish Medicines Agency (AEMPS), ISS, Institute of Marine Research, German Environment Agency (UBA), Institute of the Republic Slovenia for Nature Conservation and University of Ljubljana, Biotechnical Faculty)
- 1 industry associations (FEFANA)
- 1 private companies (Puratos)
- 3 consultant organisations (SCC Scientific Consulting Company, Pen&Tec Consulting, S.L.U. and Association of Veterinary Consultants)

NEW GUIDANCE

Guidance more structured

- More structured: different phases are clearly identified, data requirements are tabled with specific guidelines
- Better explained: questions of phase I have their own explanations; appendices provide tools and further explanations
- However clause: possibility to deviate (whenever scientifically based!) both for evaluators and applicants.
- Guidance developed for **both** the applicants **and** the evaluators

NEW GUIDANCE

Guidance more structured

NEVERTHELESS

This guidance is still a guidance, establishing major rules, unable to cover all possible situations in a risk assessment

WHICH ENVIRONMENT?

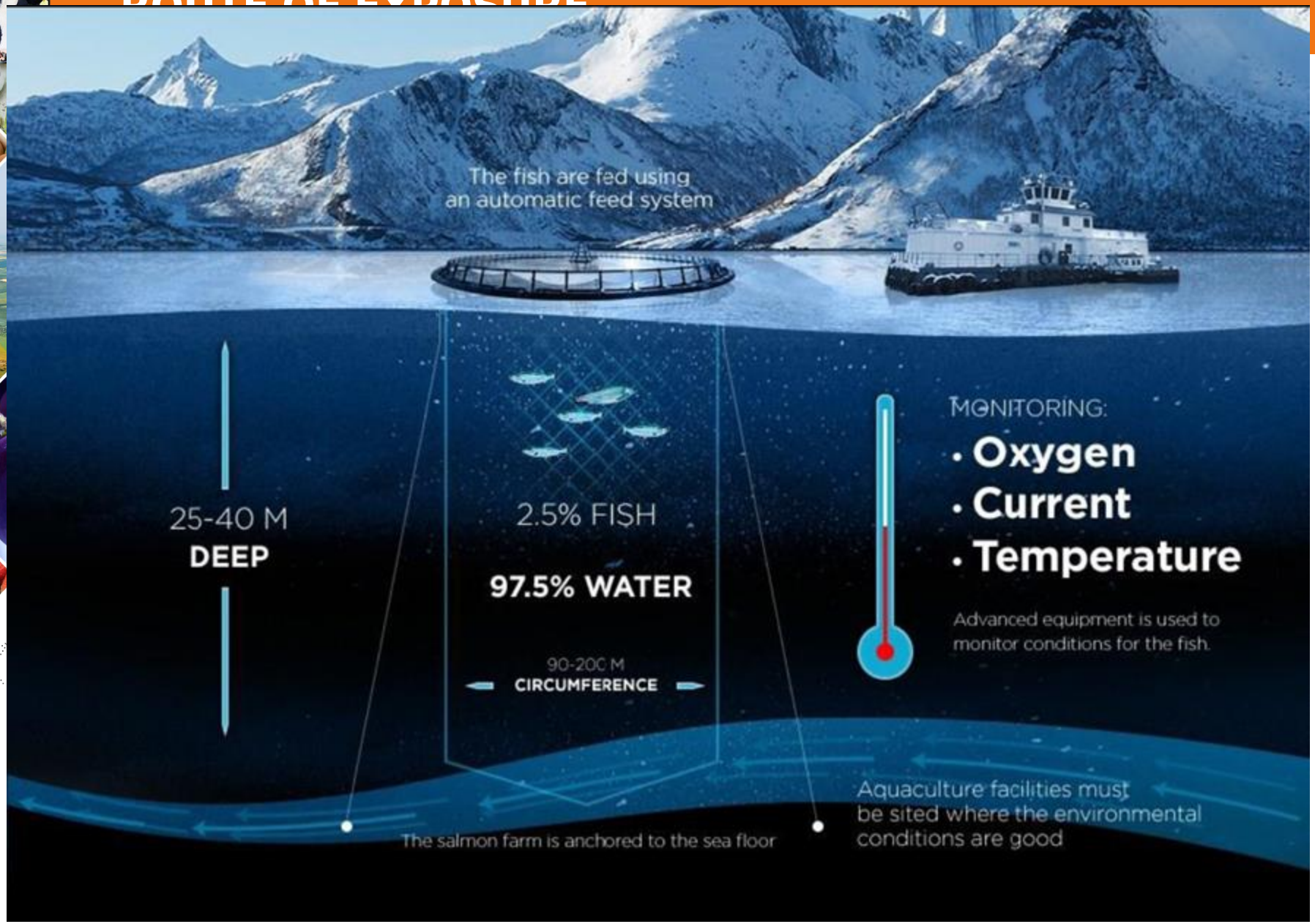
Environmental compartments to protect

- Agricultural soils that receive animal slurry contaminated with feed additives
- The water compartment of surface water (input via drainage and run-off from agricultural fields, or via land-based fish farms)
- The ground water compartment (input via leaching from soil), and
- The sediment compartment (at least for fish farmed in cages)

ROUTE OF EXPOSURE

PEC soil

ROUTE OF EXPOSURE



ROUTE OF EXPOSURE

GUIDANCE ENVIRONMENT

Two phases

Phase I

- Decision tree: exclusion criteria from a complete ERA
- Preliminary identification of problematic substances
- Screening based on exposure

Phase II

- Complete risk assessment
- Different steps of increasing complexity

The ERA of major species can be extrapolated to minor species when the same use is proposed.

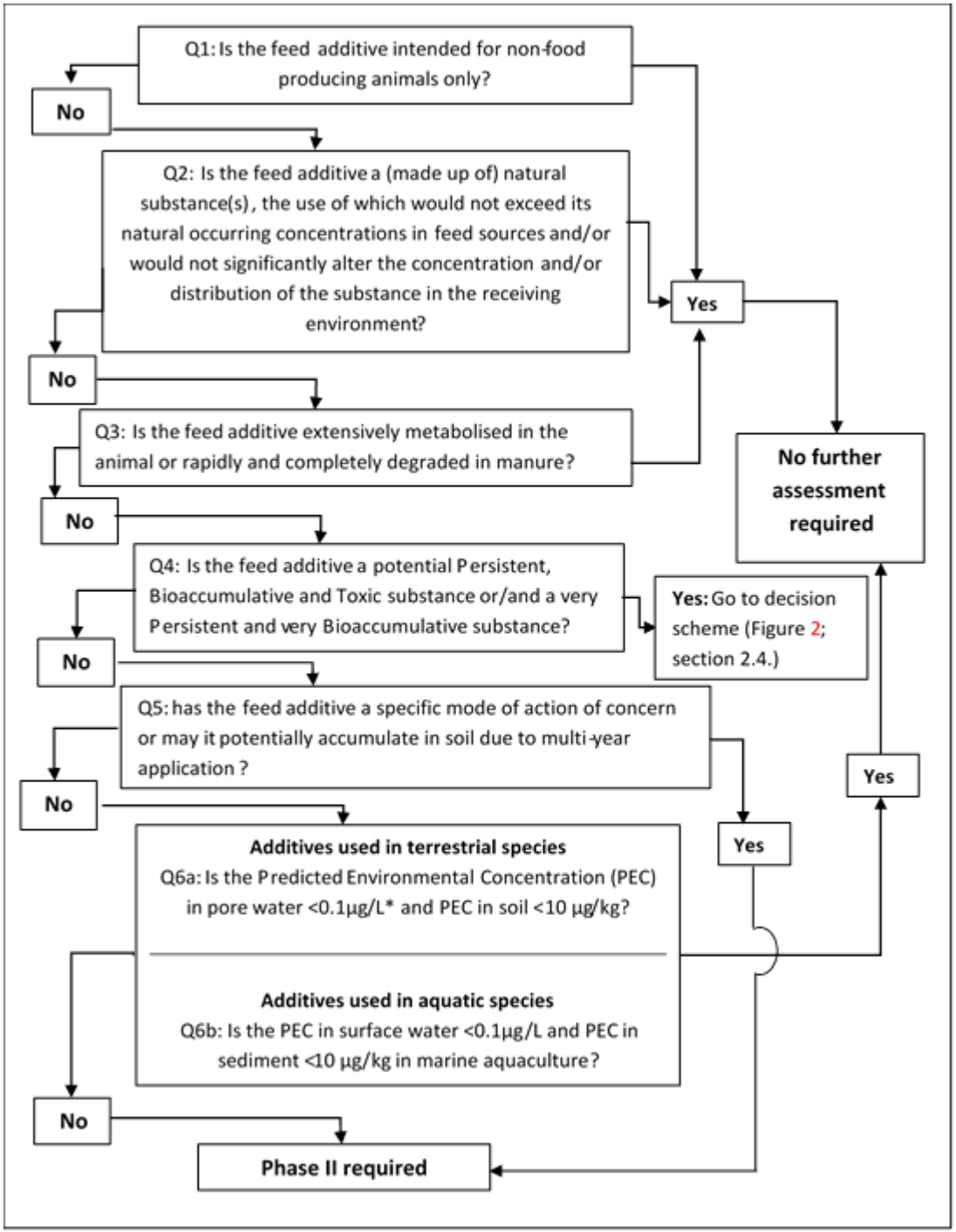
Phase I

- Phase I is based on a list of questions (decision tree).
- Questions: explanations/examples provided to clarify the meaning.
- The decision tree describes the process needed to evaluate a substance

Q1, Q2, Q3: Exclusion criteria from an ERA

Q4, Q5: identification of substances of concern

Q6: Exposure vs. trigger



PHASE I – EXCLUSION CRITERIA

Phase I: exclusion criteria

Q1: Is the additive intended for non-food producing animals only?

No

Q2: Is the feed additive a (made up of) natural substance(s), the use of which would not exceed its natural occurring concentrations in feed sources and/or would not significantly alter the concentration and/or distribution of the substance in the receiving environment?

Yes

No

Q3: Is the additive extensively metabolised in the target animal or rapidly and completely degraded in manure?

Yes

No further assessment required

PHASE I – EXCLUSION CRITERIA

Questions of Phase I

- **Question 1**: Is the additive intended for non-food producing animals only?

Generally, non-food producing animals are not intensively reared or/and their excrements are not spread over agricultural land. Therefore, due to the limited total amount of product used, feed additives for non-food animals are expected to produce less environmental concern than the feed additives in food-producing animals.

PHASE I – EXCLUSION CRITERIA

- **Question 2**: Is the feed additive a (made up of) natural substance(s), the use of which would not exceed its natural occurring concentrations in feed sources or plants that potentially occur in habitats near the receiving environment?

Evidence should be provided showing that comparable concentrations of the feed additive can be expected in other plant(s) and/or that the use of the feed additive will not significantly alter the concentration of the additive in the receiving environmental compartments of concern.

PHASE I – EXCLUSION CRITERIA

Example 1 (iron and methionine): The components of the additive, iron and methionine, are ubiquitous in the environment.

The iron content of soils is typically in the range of 5,000–50,000 mg/kg; the predicted PECsoil is around 1.75 mg/kg after a 1-year application of manure, assuming that 100% of the dose will be excreted.

Methionine as amino acid is a physiological and natural component of animals and plants.

After dissociation of the ingested additive, methionine is not excreted as such (but as urea/uric acid, sulphate and CO_2). Therefore the use of iron and methionine in animal nutrition would not lead to any localised increase in the concentration in the environment.

PHASE I – EXCLUSION CRITERIA

Astaxanthin for salmonids.

Astaxanthin in the environment is synthesised by algae. Algae contain up to XXX mg/kg carbon ….. In unfiltered sea water, natural astaxanthin is present in the range of XXX ng/L ……Shrimp can contain natural astaxanthin in the range XXXX mg/kg total dry weight ….. Natural astaxanthin accumulates in wild salmon via the food chain…. For salmon in cages to develop a red colour similar to wild salmon, they must receive a similar dose of ATX. If it would be possible to give salmon in cages the same feed as wild salmon the natural astaxanthin in the sediment would be the same. The use of synthetic ATX does not pose a significant additional risk to the environment compared with natural astaxanthin

PHASE I – EXCLUSION CRITERIA

- **Question 3**: Is the additive extensively metabolised in the target animal or rapidly and completely degradable in manure?

Extensively metabolized: converted into metabolites present in the excreta that do not possess a biological activity of environmental concern, like water, CO_2 and common salts.

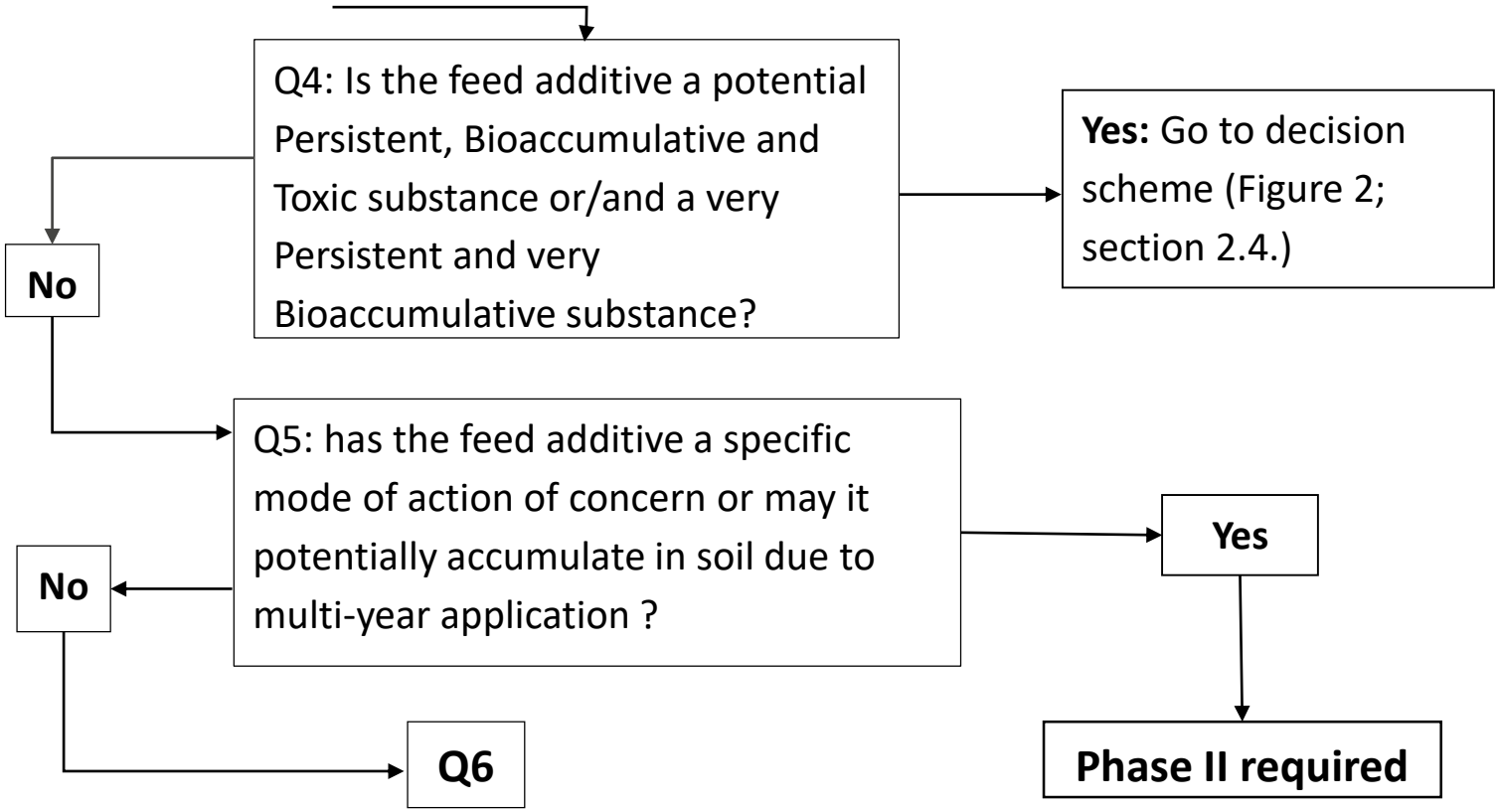
Degradation in manure.
The active substance has to be rapidly and **completely** degraded in manure (inter-species extrapolation of data can be applied):

1. total mineralisation or
2. presence of degradation products all presenting 5% or less of the dose,

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004386.pdf

PHASE I - Identification of substances of concern

Phase I: identification of substances of concern



PHASE I - Identification of substances of concern

- **Question 4**: Is the feed additive a potential PBT or/and vPvB substance?

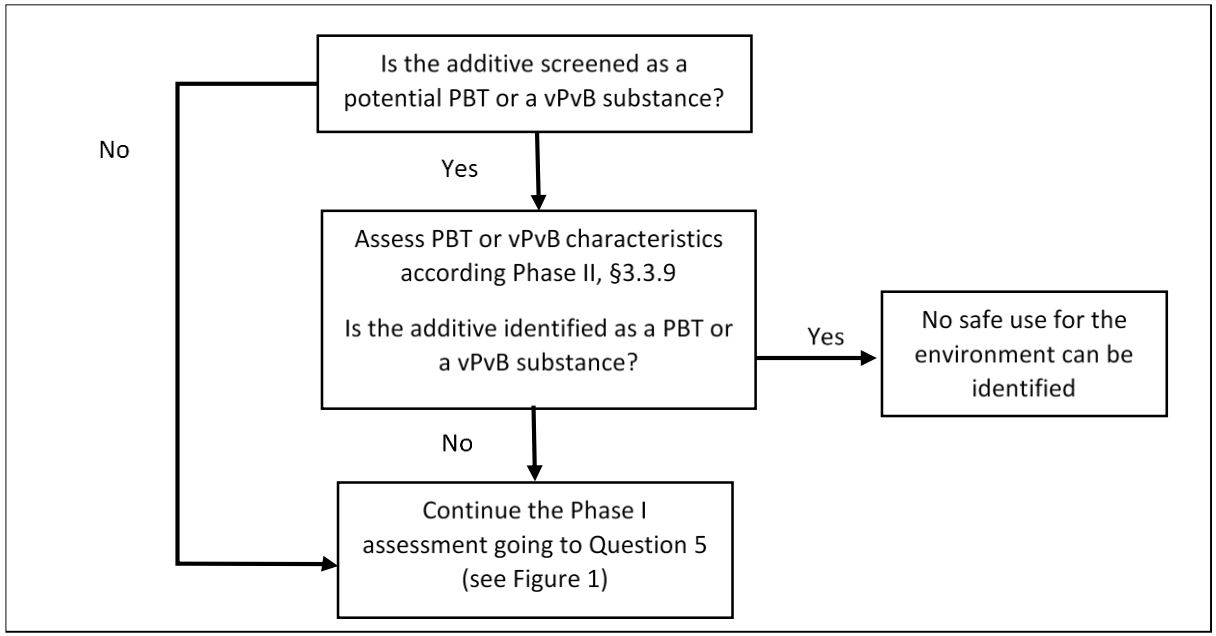
PBT/vPvB substances: potential to accumulate in parts of the environment difficult to reverse. Stop of emission not necessarily reduce chemical concentration

PBT or vPvB substances: potential to contaminate remote areas to be protected from further contamination by hazardous substances due to the intrinsic value of pristine environments

Effects of accumulation unpredictable in the long-term

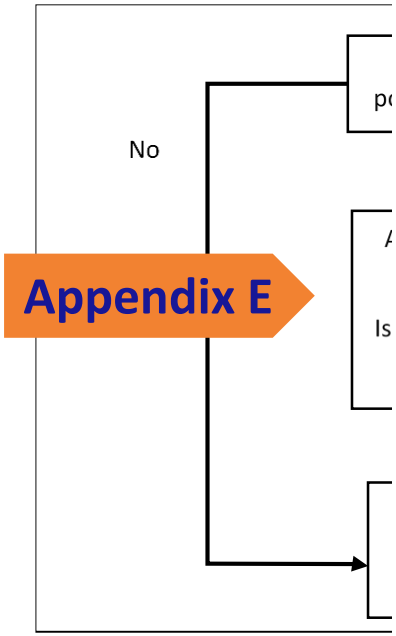
PHASE I - Identification of substances of concern

Decision scheme for PBT or vPvB



PHASE I - Identification of substances of concern

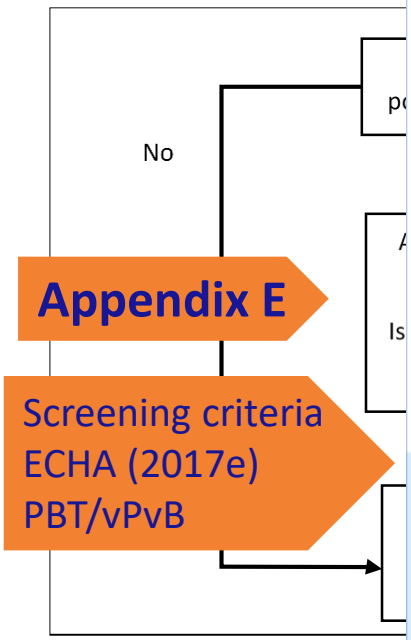
Decision s



Property	PBT-criteria	vPvB-criteria
Persistence	A substance fulfils the persistence criterion (P) in **any** of the following situations: • $T_{1/2}$ > 60 days in marine water; • $T_{1/2}$ > 40 days in fresh- or estuarine water; • $T_{1/2}$ > 180 days in marine sediment; • $T_{1/2}$ > 120 days in fresh- or estuarine sediment; • $T_{1/2}$ > 120 days in soil.	A substance fulfils the "very persistent" criterion (vP) in **any** of the following situations: • $T_{1/2}$ > 60 days in marine, fresh- or estuarine water; • $T_{1/2}$ > 180 days in marine, fresh- or estuarine sediment; • $T_{1/2}$ > 180 days in soil.
Bioaccumulation	A substance fulfils the bioaccumulation criterion (B) when: BCF > 2000	A substance fulfils the "very bioaccumulative" criterion (vB) when: BCF > 5000
Toxicity	A substance fulfils the toxicity criterion (T) in **any** of the following situations: • NOEC or EC_{10} < 0.01 mg/L for marine or freshwater organisms; • substance is classified as carcinogenic (category 1A or 1B), germ cell mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2); • there is other evidence of chronic toxicity, as identified by the classifications: STOT (repeated exposure), category 1 (oral, dermal, inhalation of gases/vapours, inhalation of dust/mist/fume) or category 2 (oral, dermal, inhalation of gases/vapours, inhalation of dust/mist/fume) according to the CLP Regulation.	-

PHASE I - Identification of substances of concern

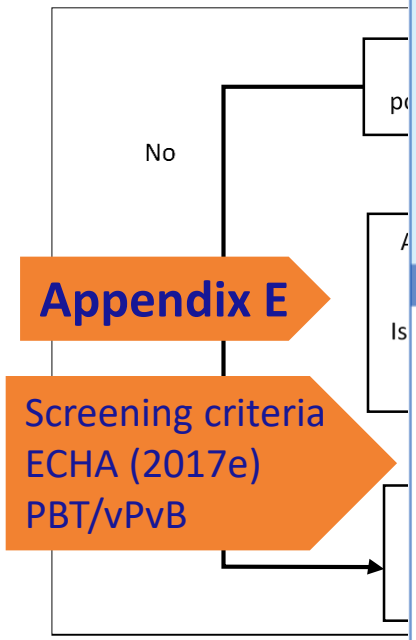
Decision s



Type of screening information	Screening criterion	Conclusion
Persistence		
Biowin 2 (non-linear model prediction) and Biowin 3 (ultimate biodegradation time)	Does not biodegrade fast (probability <0.5)[a] and ultimate biodegradation timeframe prediction: ≥ months (value < 2.25 (to 2.75)[b])	Potentially P or vP
or		
Biowin 6 (MITI non-linear model prediction) and Biowin 3 (ultimate biodegradation time)	**or** Does not biodegrade fast (probability <0.5)[a] and ultimate biodegradation timeframe prediction: ≥ months (value <2.25 (to 2.75)[b])	Potentially P or vP
or		
other models [a]	**or** Model specific values	Potentially P or vP
Ready biodegradability test (including modifications allowed in the respective TGs)	≥70% biodegradation measured as DOC removal (OECD TGs 301A, 301E and 306) or ≥60% biodegradation measured as ThCo2 (OECD TG 301B) or ThOD (OECD TGs 301C, 301D, 301F, 306 and 310) [c]	Not P and not vP
	<70% biodegradation measured as DOC removal (OECD TGs 301A, 301E and 306) or <60% biodegradation measured as ThCo2 (OECD TG 301 B) or ThOD (OECD TGs 301C, 301D, 301F,306 and 310)	Potentially P or vP
Enhanced screening tests [d]	biodegradable	Not P and not vP
	not biodegradable [d]	Potentially P or vP

PHASE I - Identification of substances of concern

Decision s



Type of screening information	Screening criterion	Conclusion
Specified tests on inherent biodegradability:		
- Zahn-Wellens (OECD TG 302B)	≥70 % mineralisation (DOC removal) within 7 d; log phase no longer than 3d; removal before degradation occurs below 15%; no pre-adapted inoculum	Not P and not vP
	Any other result [e]	Potentially P or vP
- MITI II test (OECD TG 302C)	≥70% mineralisation (O2 uptake) within 14 days; log phase no longer than 3d; no pre-adapted inoculum	Not P and not vP
	Any other result [e]	Potentially P or vP
Bioaccumulation		
Octanol-water partitioning coefficient (experimentally determined or estimated by QSAR)	Log Kow ≤ 4.5	not B and not vB [f] (in aquatic organisms)
	Log Kow > 4.5	Potentially B or vB (in aquatic organisms)
Combination of the Octanol water partitioning coefficient with the octanol air partitioning coefficient (both experimentally determined or estimated by QSAR)	Log Kow > 2 and Log Koa > 5	Potentially B (in air-breathing organisms)
Toxicity		
Short-term aquatic toxicity (algae, daphnia, fish)	EC_{50} or LC_{50} < 0.01 mg/L [g]	T criterion considered to be definitely fulfilled
Short-term aquatic toxicity (algae, daphnia, fish)	EC_{50} or LC_{50} < 0.1 mg/L [g]	Potentially T
	not biodegradable [d]	Potentially P or vP

PHASE I - Identification of substances of concern

- **Question 5**: has the feed additive a specific mode of action of concern or may it potentially accumulate in soil due to multi-year application?

Coccidiostats and histomonostats are chemicals with a **specific toxic mode-of-actio**n …….may be toxic to non-target organisms in environments that receive poultry and rabbit manure.

Substances that are very persistent or not degradable may accumulate in the receiving compartment(s). When there is already evidence (either experimental or by screening) that a feed additive is very persistent or not degradable, e.g. metals, these substances have to be assessed in Phase II.
Trigger of 10 µg/kg does not consider accumulation.

PHASE I – Exposure vs. trigger

- **Question 6a – Terrestrial animals**

  Is the Predicted Environmental Concentration (PEC) in **pore water* <0.1µg/L** and PEC in **soil <10 µg/kg**?

- **Question 6b – Aquatic animals**

  Is the PEC in **surface water <0.1µg/L** and PEC in **sediment <10 µg/kg** in marine aquaculture?

*PEC in ground water is set equal to PEC in pore water

PHASE I – Exposure vs. trigger

Exposure calculation – worst case

- Additive continuously applied at the maximum dose to the feed of the target animals;
- Total intake of the active substance is totally excreted as parent compound;
- Annual nitrogen load standard is 170 kg N/ha/y
- No dissipation of the parent compound during storage and spreading of slurry/manure;
- The additive is mixed in the soil up to 5 cm depth.

PHASE I – EXPOSURE CALCULATION

Default values for feed intake and nitrogen excretion

Animals	Body weight start-end (kg)	Productive cycles/year[1]	Feed intake (kg/animal place per year)[2]	Nitrogen excreted (kg/animal place per year)
Piglet	7-30	7.4	296	4
Pig for fattening	30-115	3.2	800	9
Sow with piglets	200	2.4	1140	23
Cattle for fattening	250-630	1.2	4050	54
Veal calf	45-250	1.5	730	11
Dairy cow [3]	650	0.92	6584	125
Lamb for fattening	4-32	1.5 [7]	273	5
Sheep for fattening	15-55	1.5 [7]	267	5
Meat sheep	60	1	607	10
Dairy sheep	60	1	580	10
Dairy goat	50	1	714	16.4
Chicken for fattening	0.045-2.2	6.5	22	0.33
Laying hen[4]	1.4-2	0.84	42	0.8
Turkey for fattening[5]	0.05-10(f)/16(m)	2.6	70	1
Rabbit for fattening	0.9-3.1	4.8	30	0.5
Horse[6]	500	1	3650	58
Horse for fattening	270-480	1.5[7]	2385	43

PHASE I – EXPOSURE CALCULATION TERRESTRIAL

PEC in soil

Concentration of the additive in feed: input data

Total feed intake (DM) per animal per year: Table 1

$$PEC_{manure} = \frac{C_{add} \times FI_{total}}{N_{excreted}}$$

Total N excretion per animal per year: Table 1

Annual nitrogen emission standard: default

$$\boldsymbol{PEC_{soil\ dw}} = \frac{PEC_{manure} \times Q}{RHO_{d\ soil} \times CONV_{area\ field} \times DEPTH_{field}}$$

Bulk density of (dry) soil: default

Default: 10000 m^2/ha

Mixing depth with soil: default 0,05 m

PHASE I – EXPOSURE CALCULATION TERRESTRIAL

PEC in soil

Concentration of the adc

Worst case PEC

- Pig for fattening
- Cattle for fattening
- Piglet
- Turkey for fattening
- Chicken for fattening
- Veal calf
- Horse
- Meat sheep
- Rabbit for fattening
- Dairy sheep
- Horse for fattening
- Lamb for fattening
- Sheep for fattening
- Dairy cow
- Laying hen
- Sow with piglets
- Dairy goat

r animal per year: Table 1

PEC

nal per year: Table 1

ission standard: default

$$PEC_{soil\ dw} = \frac{}{'H_{field}}$$

ixing depth with soil: default 0,05 m

Bulk density of (dry) soil: (

PHASE I – EXPOSURE CALCULATION TERRESTRIAL

PEC in groundwater is set equal to PEC in pore water.

Worst-case assumption, neglecting transformation and dilution in deeper soil layers.

Same simple calculations with default values.

$$PEC_{manure} = \frac{C_{add} \times FI_{total}}{N_{excreted}}$$

Mixing depth with soil: default **0.2 m**

$$\boldsymbol{PEC_{soil\ ww}} = \frac{PEC_{manure} \times Q}{RHO_{w\ soil} \times CONV_{area\ field} \times DEPTH_{field}}$$

$$\boldsymbol{PEC_{pw}} = \frac{PEC_{soil\ ww} \times RHO_{w\ soil}}{K_{soil\ water} \times 1000}$$

K_{oc}: OC partition coefficient (correlation with K_{ow} or water solubility or QSAR calculation)

VP: Vapour pressure (phys – chem or QSAR)

MOLW: Molecular weight

SOL: Water solubility (phys – chem or QSAR)

PHASE I – EXPOSURE CALCULATION

Feed ration and water flow rate in fish farming in EU

Fish types	Feed Ration (kg feed/kg fish per day)	Water flow rate (L/kg fish and day)
Salmon	0.01	**865**
Rainbow trout	0.02	**1400**
Sea bass/Sea bream	0.01	**400**
Turbot	**0.01**	**720**

PHASE I – EXPOSURE CALCULATION AQUATIC

Aquaculture: sea cages versus land-based aquaculture

Land-based fish farms: organisms living in the water column at risk from discharge to shallow freshwater ecosystems.

Simple calculations with default values.

Land-based fish farms

Concentration of the additive in feed: input data

Feed Ration

$$PEC_{swaq} = \frac{C_{add} \times FR}{Flow \times DF}$$

Water flow rate

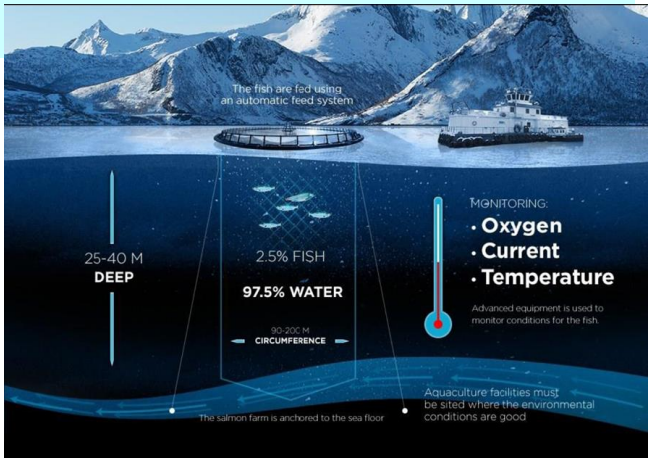
Dilution Factor

PHASE I – EXPOSURE CALCULATION AQUATIC

Aquaculture: sea cages versus land-based aquaculture

Sea cages organisms living in or on sediments are most at risk.

Simple calculations with default values.



Sea cages

Concentration of the additive in feed: input data

$$PC_{faeces} = C_{add} \times CF$$

Conversion factor (kg feed to kg total carbon in faeces)

Max deposition rate of faeces

No. of production days

$$PEC_{sed} = \frac{PC_{faeces} \times k_{dep} \times T_{production}}{RHO_{solid} \times F_{solid} \times DEPTH_{sed}}$$

Mixing depth in sed: 0.05 m

Bulk density of solids: default

Volume fraction of solids in sed

PHASE I – Exposure vs. trigger

In the last ten years, PEC calculations often performed in different ways

New EXCEL tool available onto EFSA website for harmonised PEC calculations

Phase I PEC
(soil and GW and/or SW and/or SED)

Is the trigger exceeded?

yes

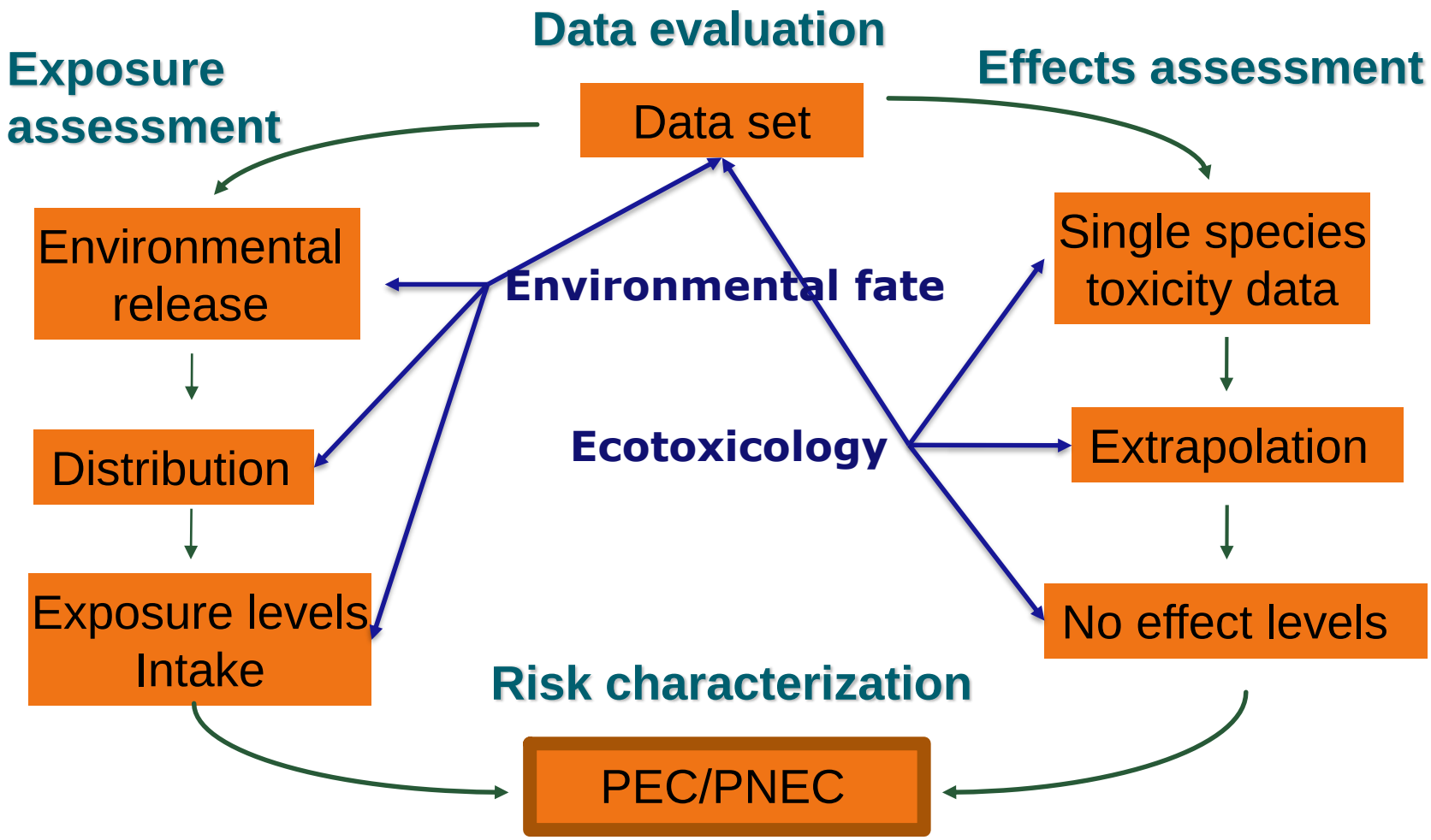
Phase II

An ERA based on experimental data is necessary

no

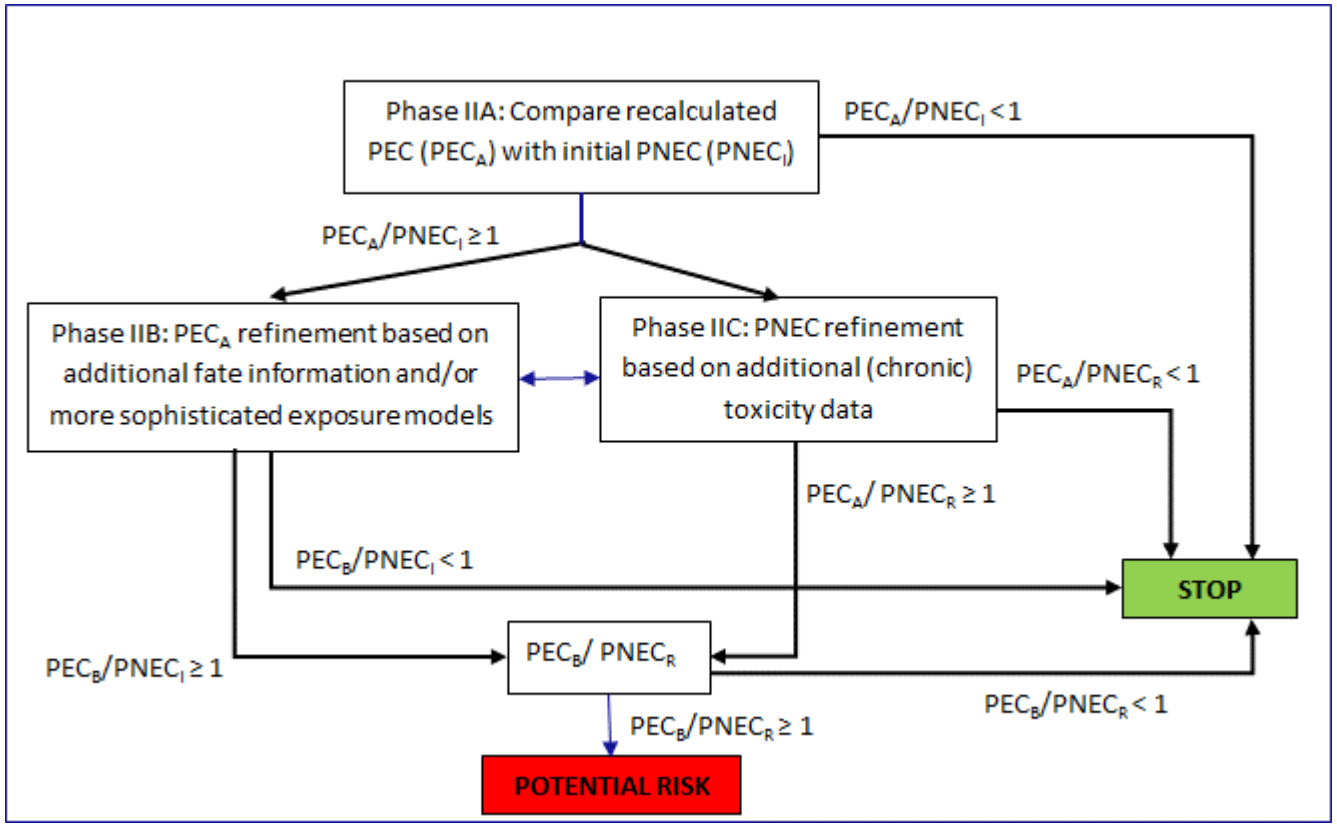
Safe use identified

ENVIRONMENTAL RISK ASSESSMENT



PHASE II ASSESSMENT

Different Steps, different complexity



PHASE II: BASE SET DATA REQUIREMENTS

Basic physico-chemical properties are needed to evaluate the fate and toxicity of the feed additive

PHYSICAL-CHEMICAL STUDIES

Water Solubility	OECD 105
Dissociation Constant	OECD 112
UV-Visible Absorption Spectrum	OECD 101
Vapour Pressure	OECD 104
n-Octanol/Water Partition	OECD 107, 117 or 123
Melting point/melting range	OECD 102

Affect distribution in different compartments

Potential to photodegrade and/or phototoxicty

May affect adsorption on soils and sediments

Calculation only, unless VP may exceed 10^{-5} Pa at 20° C.

Different guidelines depending on compound characterisctics (i.e. lipophilic)

PHASE II: ENVIRONMENTAL FATE STUDIESS

Environmental fate studies

Study	Guideline
Soil Adsorption/Desorption	OECD 106/121
Soil Biodegradation (route and rate)	OECD 307
Water/sediment degradation (route and rate, optional)	OECD 308
Photolysis in water (optional)	OECD 316
Hydrolysis (optional)	OECD 111

Required just for the terrestrial branch.

Required both for terrestrial and aquatic animals.

Required just for additives used in aquaculture or for higher tier modelling with FOCUS SW

Recommended just for additives used in aquaculture

SOIL DEGRADATION

Aerobic degradation in soil (OECD 307)

- Controlled conditions, dark, (20 ± 2° C, pF 2-2.5).
- Samples extracted and analysed for a.i, metabolites and volatiles. 120 days study.
- Soil selection: sandy loam, silty loam, loam, loamy sand; pH=5.5-8; OC%=0.5-2.5%

Critical points:

High recovery in the study
At least 4 soils, to use a geomean value
DT_{50} derived according SFO (FOCUS guideline)

WHICH KINETICS?

Which criteria?

- The SFO kinetics, where possible, is the preferred mode for deriving a proper DT_{50}
- For PEC calculations:
  - **Geometric mean value** when there are no dependence on soil properties such as clay or pH.
  - Parameters derived by **best-fit kinetics** from lab (**normalised to 12°C**). If not SFO, longest phase to be used
- As input for exposure modelling of higher tier:

  Geometric mean value derived by **SFO kinetics** from laboratory (**normalised to 20°C**); for higher-tier modelling also bi-phasic kinetics possible.

ADSORPTION TO SOIL

Soil adsorption/desorption studies (OECD 106)

- K_d : distribution coefficient, simple ratio of sludge or soil to solution concentration at equilibrium

$$Kd = \frac{Csoil}{Cwater}$$

- For neutral organic compounds often the Kd is related to the organic content of sludge or soil. In these cases the Kd is normalised

$$Koc = \frac{Kd}{\text{percentage organic carbon}} \times 100$$

- Aim: to determine the strength of sorption of a.s. to soil

ADSORPTION TO SOIL

Soil adsorption/desorption studies (OECD 106)

CRITICAL POINTS

- ❑ High recovery range for labelled substances
- ❑ At least 4 soil to be selected according to the guidance
- ❑ Attention when:
  - Active substance shows a weak sorption
  - Active substance is adsorbed on the test vessel
  - Active substance declines during the study

ADSORPTION TO SOIL

OECD 121

- Useful for chemicals difficult to study (i.e. substances volatile, not soluble in water at a concentration which can be measured analytically, with a high affinity to the surface of incubation systems
- A minimum of six reference points, at least one above and one below the expected value of the test substance should be used.

More reliable than a QSAR evaluation

PHASE II A PEC– TERRESTRIAL ANIMALS

Phase I PEC recalculation

Experimental data: may lower or increase PECs

Recalculation based on metabolism

Reduction of excreta:
lower PEC_{soil}
lower PEC_{sw}
lower PEC_{gw}

Recalculation based on degradation in soil for persistent compound ($PEC_{soil\ plateau}$)

higher PEC_{soil}
higher PEC_{sw}
higher PEC_{gw}

Recalculation based on DT_{50} in soil under multiple applications

Applicable in few cases;
lower PEC_{soil}

PHASE II A PEC– TERRESTRIAL ANIMALS

Phase I PEC recalculation

Groundwater

- Recalculation PEC_{pw} and $PEC_{pw\ plateu}$

Surface water and sediment

- PEC_{sw}= 1/3 $PEC_{groundwater}$
- PEC_{sed} from PEC_{sw} – Equilibrium partitioning

PHASE II A PEC– AQUACULTURE

Phase I PEC recalculation

Aquaculture (freshwater and marine)

- There are no advanced models accepted at EU level which can be suggested for the refinement of the exposure for marine and freshwater aquaculture.
- In Phase I it is assumed that there is no retention in the system.
- In Phase II, for freshwater aquaculture, this could be considered as a further PEC refinement.
- An applicant could also present further assessment, using other modelling tools, more studies or relevant arguments provided that these models, studies and/or arguments are scientifically underpinned.

ENVIRONMENTAL RISK ASSESSMENT

Data evaluation

Data set

Exposure assessment

Environmental release

Distribution

Exposure levels Intake

Environmental fate

Effects assessment

Single species toxicity data

Extrapolation

No effect levels

Risk characterization

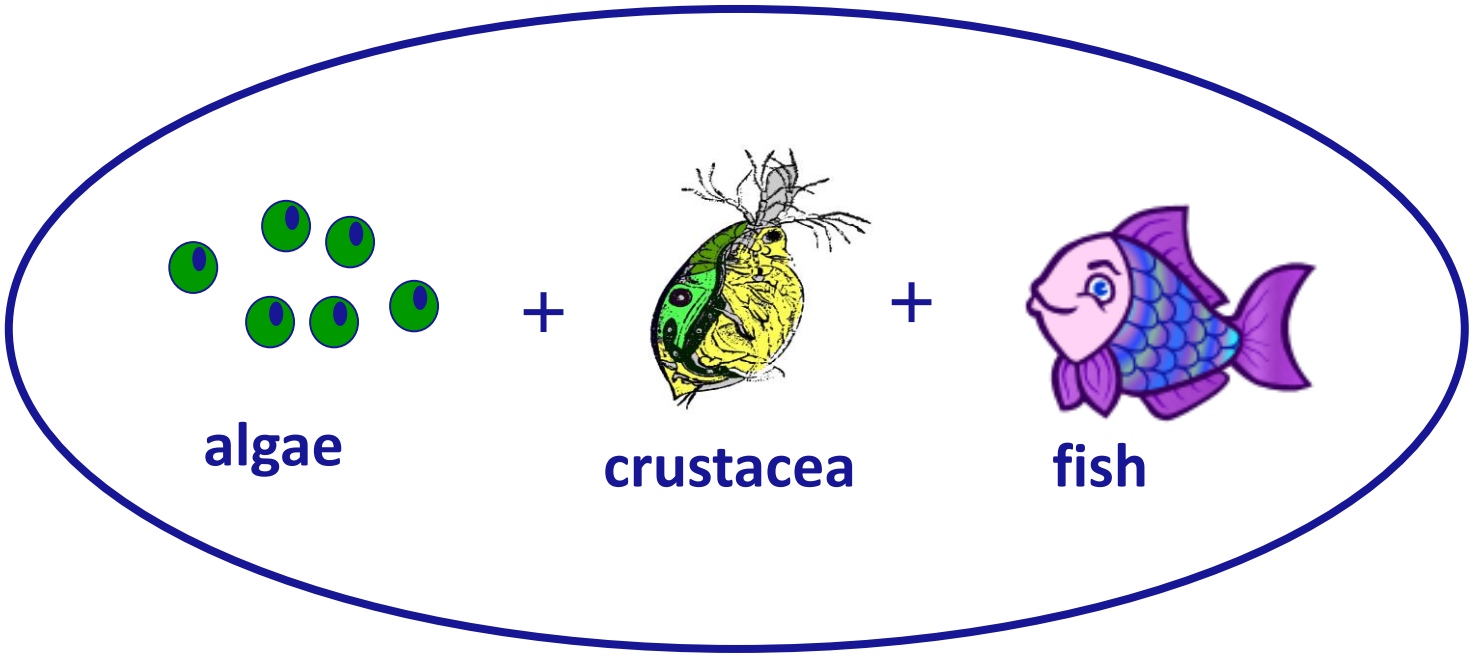
PEC/PNEC

DIFFERENCES BETWEEN TOX AND ECOTOX

		Toxicology	Ecotoxicology
Methods	**Tests on a small number of indicator organisms** ***Extrapolation to***	**Rat, rabbit, dog, monkey, etc.** **A single species (man)**	**Aquatic (algae, Daphnia, Fish)** **Terrestrial (plants, bee earthworm, birds)** **All existing species of biological communities and ecosystems**
Objectives		**Protection of individuals**	**Maintaining structure and function of ecosystems**

PHASE II A: EFFECT ASSESSMENT

- various trophic levels
- laboratory testing (single species; standardised test)



PHASE II A: EFFECT ASSESSMENT

ERA - Considered organisms

Terrestrial Organisms

-Earthworms

-Soil micro-organisms

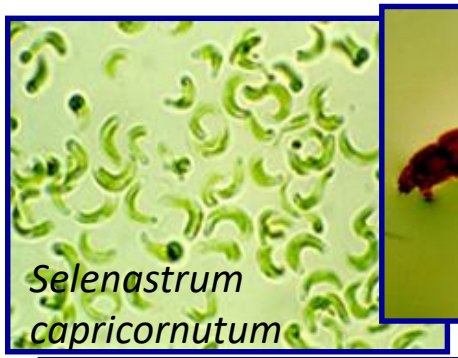
-Non-target plants

Aquatic Organisms

-Fish

-Aquatic invertebrates

-Algae



Sediments

Sediment dwellings

PHASE II A: EFFECT ASSESSMENT

Predicted No Effect Concentration (PNEC)

Critical review of the reliability of test results (often based on OECD criteria)

An extensive literature search may provide information on the safety of the feed additive under the proposed conditions of use for the environment.

Selection of key studies with lowest reliable LC_{50}/ EC_{50}/ NOEC

Application of Appropriate Assessment Factor (1000/100/50/10)

PHASE II A: EFFECT ASSESSMENT

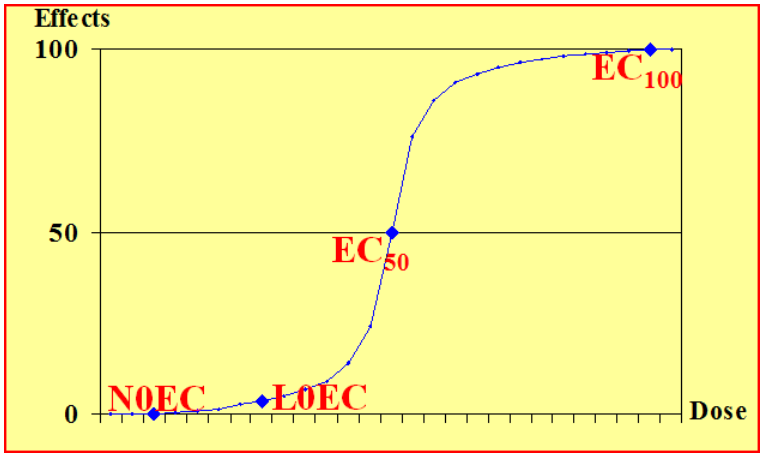
Predicted No Effect Concentration (PNEC)

Why a safety factor?

- Variation intra- and inter-species
- Variation intra- and inter-laboratory
- Extrapolation short-term to long-term
- Extrapolation laboratory to field
  - bioavailability, ageing
  - competition, food web interaction
  - adaptation, recovery

PHASE II A: EFFECT ASSESSMENT

Acute toxicity tests



Laboratory defined & controlled conditions

- Range of test concentrations, doses, rates + control(s) or limit test
- Covers range 100 to 0 % effect (often, but not always mortality)
- Endpoints: LC/EC_{50} - LD_{50} – LR/ER_{50} (Conc which is expected to produce an effect in 50% of the test population)

PHASE II A: EFFECT ASSESSMENT

Terrestrial environment

Study	Toxicity endpoint	AF	Remark
Nitrogen Transformation (28 days) – **OECD 216**	≤25% of control	1	Exposure 1X and 10X PEC_{max}
Terrestrial plants (14-21 d) **OECD 208**	EC_{50}	100	The most sensitive endpoint (emergence, biomass or height of sprout) of all plant species tested
Earthworm acute (14 d) **OECD 207**	LC_{50}	1,000	-

PHASE II A: EFFECT ASSESSMENT

OECD 207 – Earthworms

LC_{50} mg/kg dry weight soil

Test duration: 14 days

One concentration resulting in no mortality and one resulting in total mortality should be used

Validity criteria: mortality in the controls ≤10 %

PHASE II A: EFFECT ASSESSMENT

OECD 208 – Terrestrial plants

- 6 species (at least two monocot and two dicot species)
- Duration: 14-21 days after 50% control plants emerged
- Validity criteria: control seedling emergence ≥ 70%, no visible phytotoxic effects mean survival of emerged seedlings ≥ 90%
- Endpoints: emergence, mortality, growth (weight, height), visual phytotoxicity

PHASE II A: EFFECT ASSESSMENT

OECD 216 - Nitrogen Transformation

Decisive parameter: the magnitude of effects compared to the untreated control, and the time-course of recovery.

The critical level is ≤25% difference from control after 28 days.

Larger deviation will require further refinement.

It is recommended to compare directly the test concentrations to the PEC values before to conclude on potential risk.

PHASE II A: EFFECT ASSESSMENT

Freshwater compartment (including sediment)

Study	Toxicity endpoint	AF	Remark
Algal growth inhibition* **OECD 201**	72h E_rC_{50}**	1,000	E_yC_{50}*** may be used if E_rC_{50} not reported
Daphnia immobilization **OECD 202**	48-h EC_{50}	1,000	-
Fish acute toxicity **OECD 203**	96-h LC_{50}	1,000	-

* In case problems arise with coloured additives, *Lemna* (OECD 221) can be used

** E_rC_{50}: the concentration of test substance which results in a 50 percent reduction in growth rate;

*** E_yC_{50}: the concentration of the test substance with results in a 50% reduction of yield.

PHASE II A: EFFECT ASSESSMENT

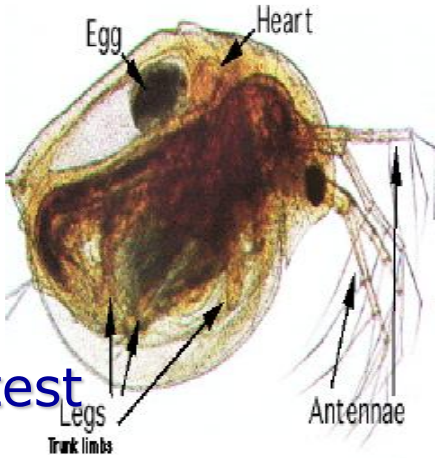
OECD 201: Freshwater alga

- At least 5 tested concentration plus control, 3 replicates per treatment
- Duration 72 h
- Endpoint: growth rate inhibition E_rC_{50}
- Validity criteria:
  - Exponential growth of biomass in control (at least 16× in 72-h
  - Coefficient of variation of control groth rate <7%
- Analytical measurements mandatory (pH, oxygen, test substance)

PHASE II A: EFFECT ASSESSMENT

OECD 202: *Daphnia magna* acute

- At least 5 tested concentration plus control, 4 replicates for tested level, 5 daphnids for replicate.
- Duration: 48 h
- Validity criteria:
  - mortality in control ≤ 10%
  - dissolved oxygen ≥ 3 mg/L in control and test vessel
- Considered observations: immobilisation (EC_{50}).
- Analytical measurements mandatory (pH, oxygen, test substance)



PHASE II A: EFFECT ASSESSMENT

OECD 203 – Fish acute toxicity test

- At least 5 tested concentration plus control, 7 fish for tested level.
- Validity criteria:
  - mortality in control ≤ 10%
  - constant conditions maintained
  - dissolved oxygen at least 60%
- Endpoint: mortality (LC_{50})
- Analytical measurements mandatory (pH, oxygen, test substance)

PHASE II A: EFFECT ASSESSMENT

Sediments

log K_{oc} or log K_{ow} ≥ 3 for an organic chemical: **trigger value for sediment effect assessment**.

$PNEC_l$ for freshwater sediment-dwelling organisms derived on basis of the Phase IIA $PNEC_l$ for aquatic organisms and through Equilibrium Partitioning (EqP) concept

$$PNEC_{sed} = \frac{K_{susp-water}}{RHO_{susp}} \times PNEC_{surface\ water} \times 1000 \times CONV_{susp}$$

K_{oc}

Substance specific

PHASE II A: EFFECT ASSESSMENT

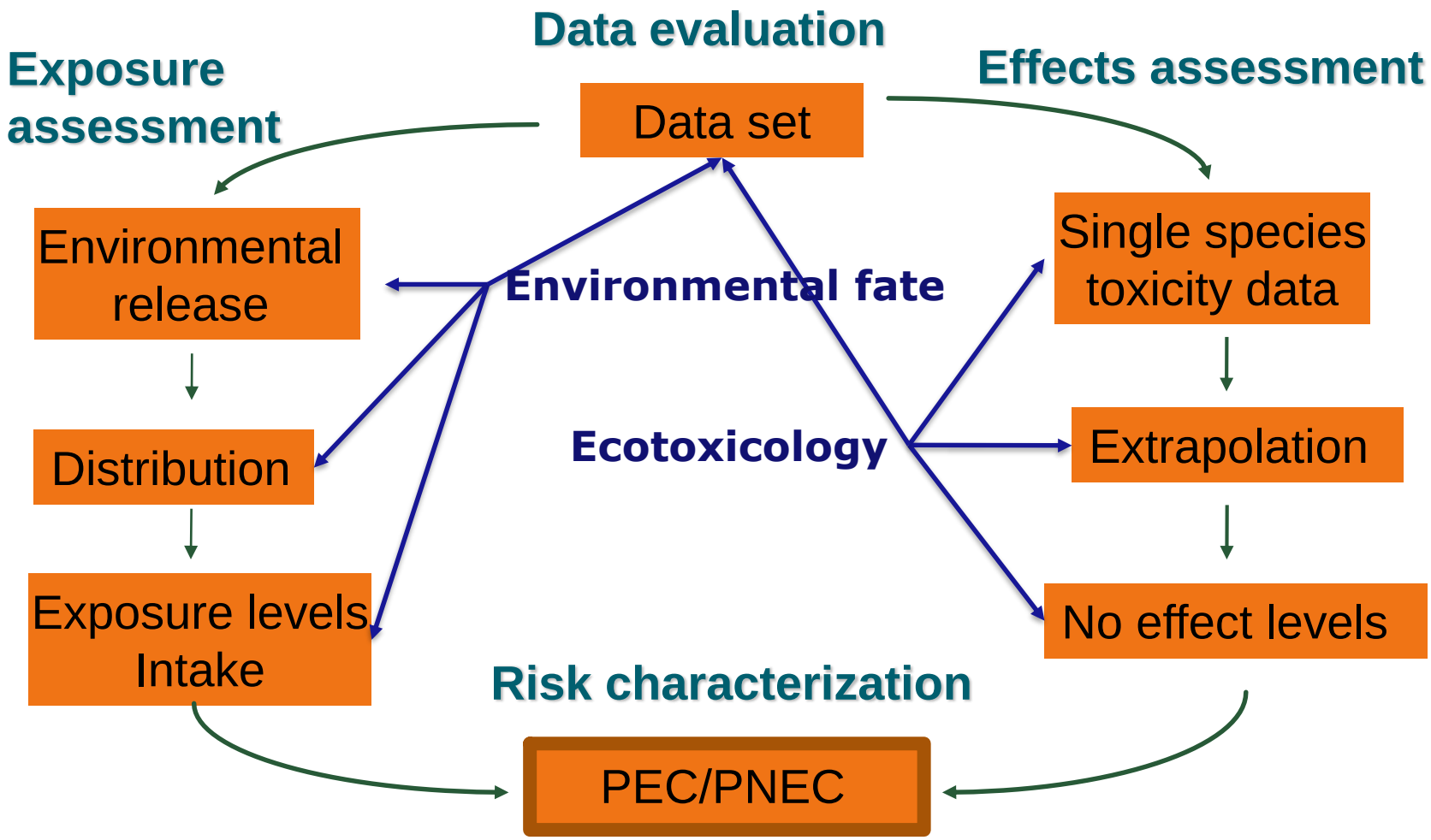
Invertebrates in marine environment

Study	Toxicity endpoint	AF	Remark
***Corophium volutator* (ISO 16712)**	10-d LC_{50}	1,000	Recommended marine species
Second marine/estuarine benthic species (Table 8)*	10-d LC_{50}	1,000	At least another taxonomic group than Crustacea is required in the data set
Third benthic marine/estuarine or freshwater species (Table 8 and 9)*	10-d LC_{50}	1,000	At least another taxonomic group than Crustacea is required in the data set

*If in the near future ISO and/or OECD guidelines for short-term toxicity tests with marine/estuarine bentic species become available, these protocol tests are preferred.

10 days duration, 3 replicates
Validity criteria: control survival (mean)≥85%
Endpoint: mortality (LC_{50})

ENVIRONMENTAL RISK ASSESSMENT

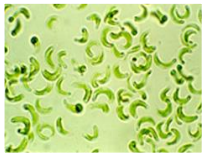
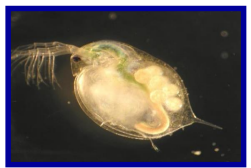


WHICH PEC? WHICH PNEC?

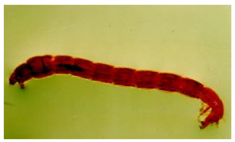

Terrestrial animals


PEC_{soil} → $PNEC_{terrestrial}$


PEC_{sw} → $PNEC_{aquatic}$

PEC_{sed} → $PNEC_{sed}$ → EqP



PEC_{gw} → 0.1 µg/L

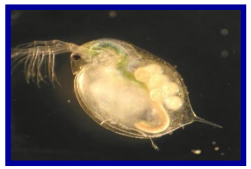
WHICH PEC? WHICH PNEC?

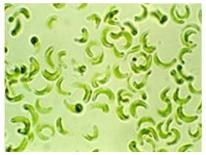
Aquaculture

Land-based aquaculture

PEC_{swaq}

$PNEC_{aquatic}$





Sea cages

$PEC_{marine\ sed}$

$PNEC_{sed}$

WHICH PEC? WHICH PNEC?

Proper comparison between the PEC_{soil} and /or PEC_{sed} and relative PNEC

Correction for soil properties: the toxicity tests underlying the PNEC need to be normalised to the OC content used to derive the PEC soil

Correction for sediment OC content: properties the toxicity tests underlying the PNEC need to be normalised to the OC content of suspended solids used to derive the PEC sediment

PHASE II A

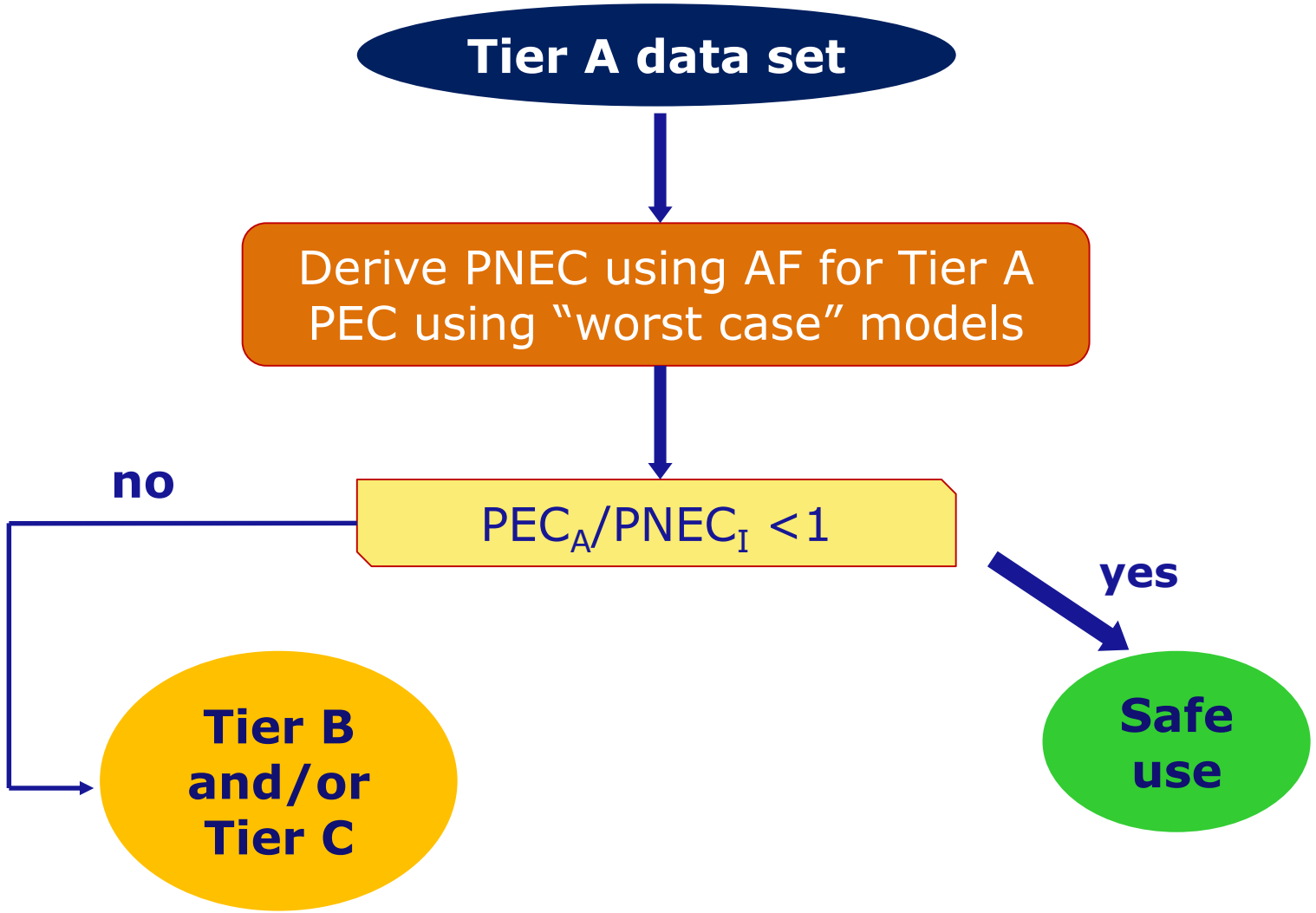
Risk assessment for secondary poisoning

If a substance has a log Kow ≥ 3 the risk for secondary poisoning (food web transfer) has to be assessed.

QSAR evaluation for BCF

Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38, Rev. 1

PHASE II A: RISK CHARACTERISATION



PHASE II B: EXPOSURE REFINEMENT

PEC_B refinement for soil

Refinement based on degradation in manure (EMA Guideline 2011)

PEC_{manure} to be calculated for a storage time similar to one animal production cycle

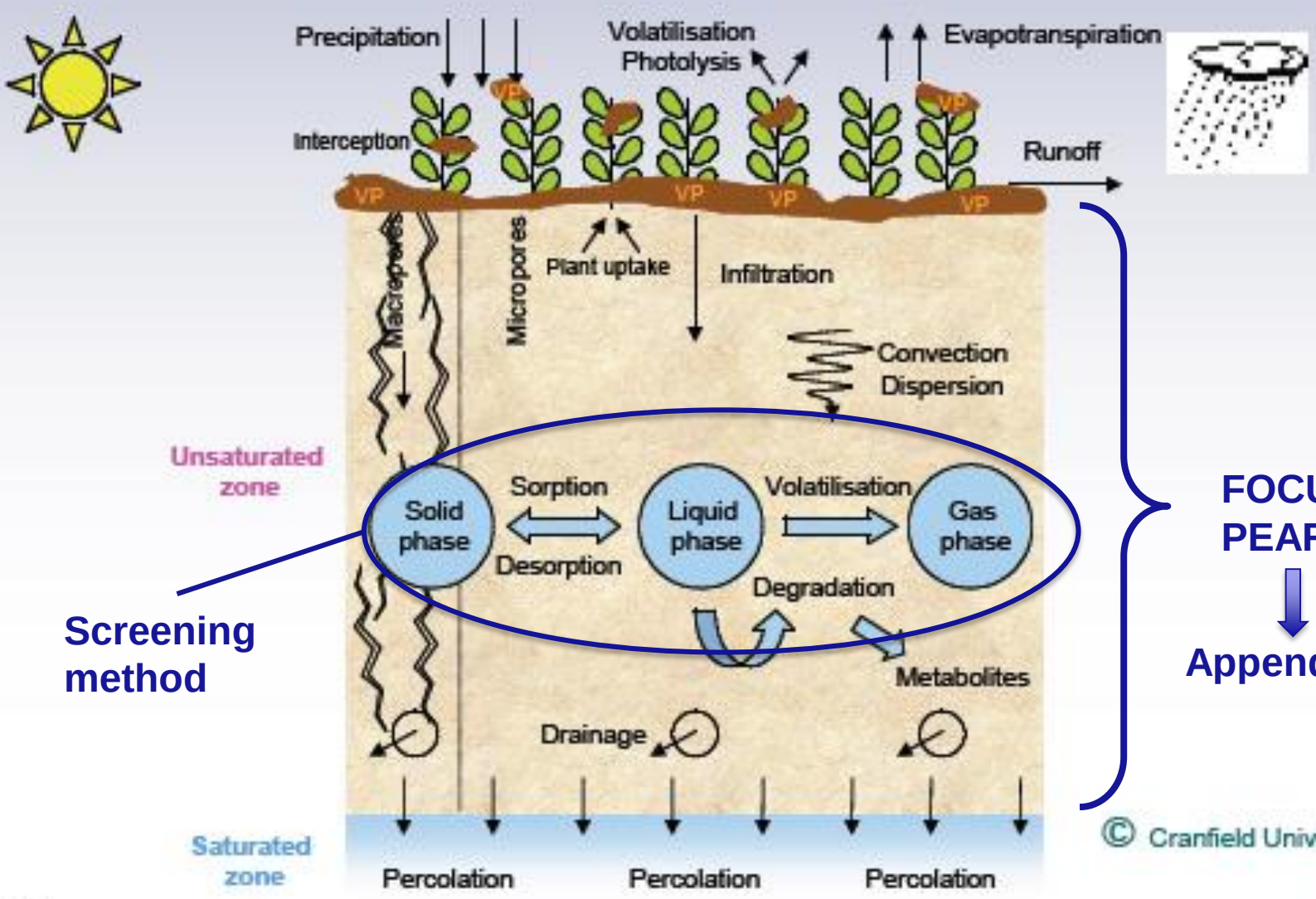
PEC_B refinement for groundwater

C_{FOCUS} (µg L^{-1})	Requirement for the K_{OM}
<0.001 - 0.01	$K_{OM} > -5.9 + 9.1\ DT_{50}$
0.01 - <0.1	$K_{OM} > -5.9 + 6.5\ DT_{50}$
≥0.1 – 1	$K_{OM} > -5.9 + 3.8\ DT_{50}$
1 – 10	$K_{OM} > -5.9 + 1.2\ DT_{50}$

Higher PEC_B refinement for GW/SW

FOCUS modelling

Fate and transport processes in soil



FOCUS GW

https://esdac.jrc.ec.europa.eu/projects/ground-water

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Ground Water

The FOCUS groundwater scenarios became available around 1 January 2001. They are used to assess the potential movement of active substances and metabolites of plant protection products to groundwater. They form a part of the review process for active substances in the EU in the context of Directive 91/414/EEC.

- OVERVIEW
- DOCUMENTATION

Related Content

MACRO | PEARL | PELMO | PRZM_GW | Model Correspondence

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FOCUS GW

https://esdac.jrc.ec.europa.eu/projects/ground-water

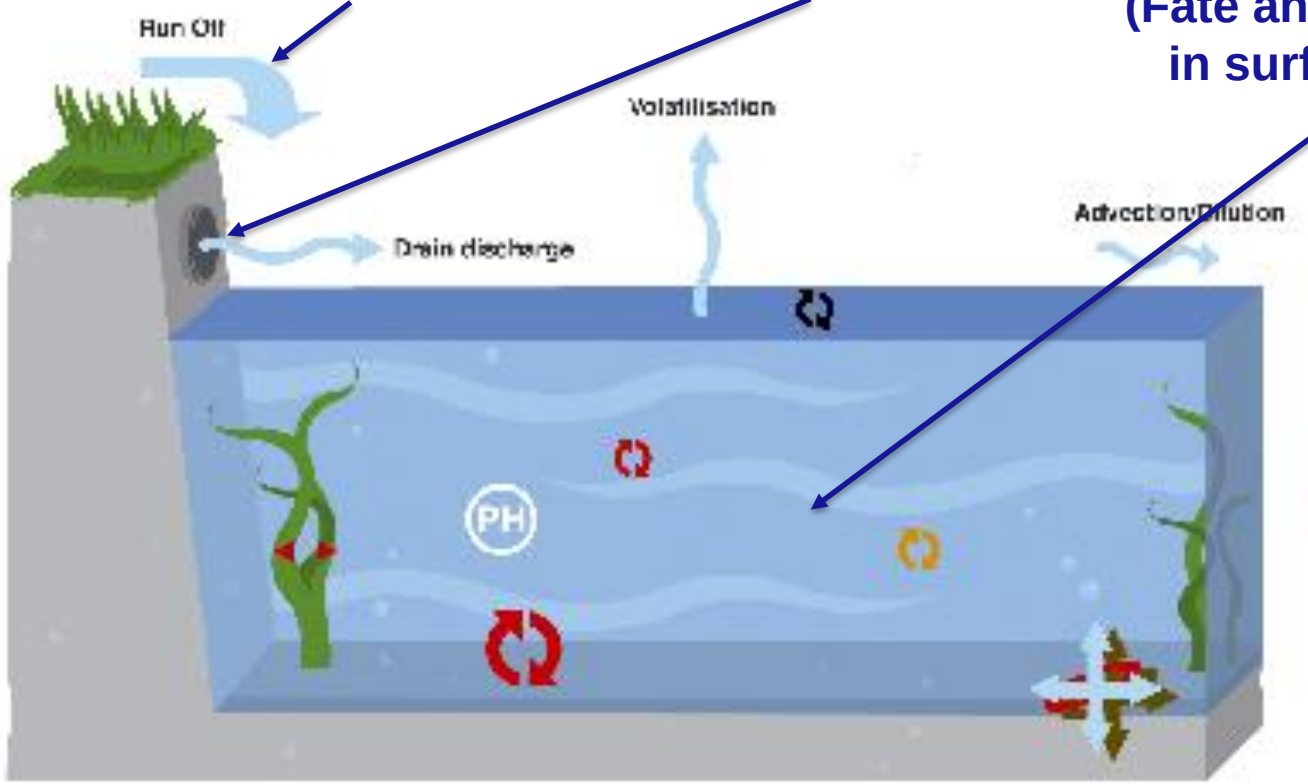
PHASE II B: EXPOSURE REFINEMENT

FOCUS surface water models

PRZM (Run-off)

MACRO (Drainage)

TOXSWA (Fate and behaviour in surface water)



Appendix C

- Sorption/Desorption
- Biodegradation
- Macrophyte Partitioning
- Dissociation
- Hydrolysis
- Photolysis

FOCUS MODELS

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Surface Water

Surface water is the second environmental compartment covered by the activities of FOCUS.

The possibilities of contamination of surface waters by the application of plant protection products (PPP) are already recognised for a long time. Main processes involved in the loading of surface waters with plant protection products are e.g. drift, drainage and run-off. The estimation of the concentration of the active substance of PPP is therefore required in the registration process in the European Union according to Directive 91/414/EEC.

The activities to determine the Predicted Environmental Concentration (PEC) in surface waters were distinguished into two parts. Firstly, the inventory of possible mathematical models suitable for this task and secondly, the development of a tiered approach to estimate these PECs for the benefit of the registration. The first part has been carried out from 1995 through 1996 and the second part from 1997 through 2002 (see Documentation of FOCUS Surface water).

OVERVIEW

DOCUMENTATION

Related Content

STEPS_ONE_TWO | SPIN | SWASH | MACRO | PRZM_SW | TOXSWA | Drift Calculator | Model Correspondence

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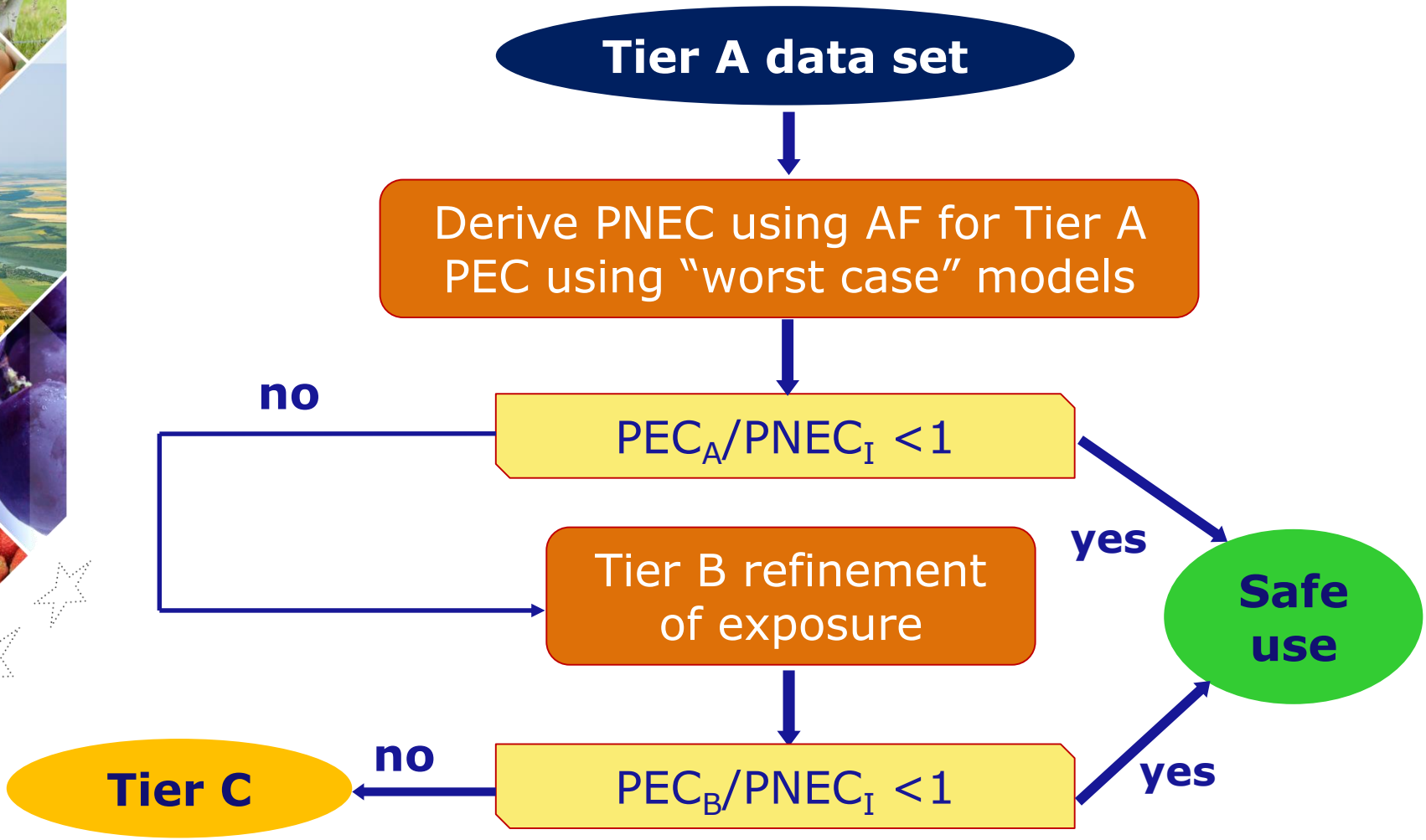
FOCUS DG SANTE

PHASE II C: EFFECT REFINEMENT



PHASE II C: EFFECT REFINEMENT

ERA – Chronic Toxicity Testing

Chronic – long-term lab studies

- Range of test concentrations (rates/doses) + control, maybe chosen by range finding or acute toxicity data, rarely done as limit tests
- Endpoints: EC_{10}/NOEC/LOEC based on survival, growth, development, reproduction (ecologically relevant parameters)

PHASE II C: EFFECT REFINEME

Duration 56 days
EC_{10}/NOEC
28 days *(*growth and *m*ortality),
56 days reproduction

$PNEC_R$ derivation for s

Study	Toxicity endpoint	AF	Remark
Terrestrial plants	14-21d EC_{10} (or NOEC)	10	Most sensitive end point of all tested species
Earthworm subacute/reproduction **OECD 220/222**	56-d EC_{10} (or NOEC)	10	
Collembolan reproduction test **(OECD 232) or** Predatory mite reproduction test **(OECD 226)**	28-d EC_{10} (or NOEC) 14-d EC_{10} (or NOEC)	10	not required if the EC_{10}/NOEC of most sensitive plant is at least 10 times lower than that of the earthworm
Nitrogen Transformation **(100 days)**	≤25% of control	1	Exposure 1x and 10x PEC_{max} Section 3.5.1.3

Same study of Phase IIA, different endpoint (EC_{10})

Same study of Phase IIA, longest period

Recommended
Hypoaspis aculeifer
14 days
Mortality, reproduction
(EC_{10}/NOEC)

Recommended
Folsomia candida
28 days
Mortality, reproduction
(EC_{10}/NOEC)

PHASE II C: EFFECT REFINEMENT

$PNEC_R$ derivation: fresh water compartment

Study	Toxicity endpoint	Remark
Algal growth inhibition **OECD 201**	72-96 h E_rC_{10} or NOE_rC	E_yC_{10} or NOE_yC may be used if E_rC_{10} or NOE_rC not reported
Daphnia reproduction **OECD 211**	21-d EC_{10} or NOEC	
Fish early life-cycle test **OECD 210**	EC_{10} or NOEC	Duration of test dependent on test species

Same study of Phase IIA, different endpoint (E_rC_{10})

Duration: 21 days
Number of offspring per parent at the end of test (EC_{10}/NOEC)

Duration: variable
Success in hatching and survival; growth (lenght/weight) behaviour and development (EC_{10}/NOEC)

PHASE II C: EFFECT REFINEMENT

$PNEC_R$ derivation: fresh water compartment

Available data	AF	Remark
One long-term EC_{10}/NOEC algae	100	An AF of 100 to the EC_{10} (NOEC) of the algae can only be applied if based on acute $L(E)C_{50}$ data there is evidence that algae are at least one order of magnitude more sensitive than Daphnia and fish.
Two long-term EC_{10}/NOECs (algae and *Daphnia* or fish)	50	Species tested should cover the most sensitive from the acute data set (Section 3.3.6.2). The lowest value should be used to derive the PNEC
Three long-term EC_{10}/NOECs	10	The lowest value should be used to derive the PNEC

PHASE II C: EFFECT REFINEMENT

$PNEC_{R;sed}$ for freshwater sediment-dwelling organisms

EqP approach based on the PNEC for freshwater pelagic organisms revised based on the Phase IIC $PNEC_{R;sw}$

When a risk is triggered

Experimental studies

PHASE II C: EFFECT REFINEMENT

$PNEC_{R;sed}$ for freshwater sediment-dwelling organisms

Study	Toxicity endpoint	Remark
Sediment-Water Chironomid Toxicity Test	28-d EC_{10} or NOEC	OECD 218
Sediment-Water Lumbriculus Toxicity Test	28-d EC_{10} or NOEC	OECD 225
Chronic test with other benthic freshwater or marine/ estuarine species	EC_{10} or NOEC	Table 19

Available data	AF	Remark
One long-term EC_{10}/NOEC (Chironomus)	100	Sediment-Water Chironomid Toxicity Test currently is a data requirement
Two long-term EC_{10}/NOEC (Chironomus and Lumbriculus)	50	-
Three long-term EC_{10}/NOECs (Table 19 of the guidance)	10	Overview of freshwater and estuarine or marine benthic test species for which protocol tests are available

PHASE II C: EFFECT REFINEMENT

$PNEC_{Rsed}$ derivation: Marine compartment

Study	Toxicity endpoint	Remark
Marine/estuarine crustacean	EC_{10} or NOEC	
Second marine/estuarine benthic invertebrate	EC_{10} or NOEC	At least another taxonomic group than Crustacea is required in the data set
Third benthic marine/estuarine or freshwater invertebrate	EC_{10} or NOEC	At least another taxonomic group than Crustacea is required in the data set

Available data	AF	Remark
One long-term EC_{10}/NOEC	100	Species tested should cover the most sensitive species from the acute data set (Section 3.3.6.3)
Two long-term EC_{10}/NOEC values (different taxonomic groups)	50	Species tested should cover the most sensitive species from the acute data set (Section 3.3.6.3).
Three long-term EC_{10}/NOECs	10	Table 20

PHASE II C: REFINEMENT

Risk assessment for secondary poisoning

The QSAR estimate of the BCF value can be replaced by an experimental value determined in a study conducted according the OECD TG 305 to further refine the assessment of secondary poisoning when in phase IIB still a risk has been identified

PHASE II C: EFFECT REFINEMENT

Derive PNEC using AF for Tier A
Estimate PEC using "worst case" models

$PEC_A/PNEC_I$ <1

NO!

YES

Tier B: exposure refinement

Refine PEC based on metabolism and/or degradation and/or more realistic models

$PEC_B/PNEC_I$ <1

YES

STOP

NO!

Tier C chronic studies

Derive PNEC using AF for Tier B

$PEC_B/PNEC_R$ <1

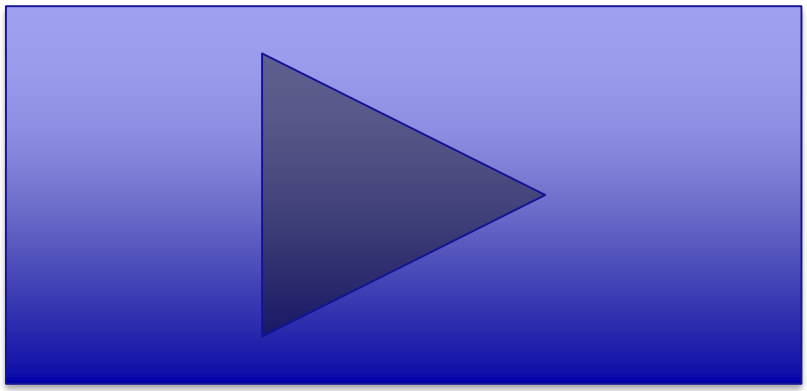
YES

NO!

Higher tier studies or risk mitigation!

EXCEL TOOL

Same model, same results

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