Practical examples on active substance risk assessment: Fungicides

Theo Brock, Alterra, Wageningen UR (PPR Panel Member)

Practical examples

Aim to illustrate the most important items of the guidance provided in the new AGD

Focus of this presentation on:

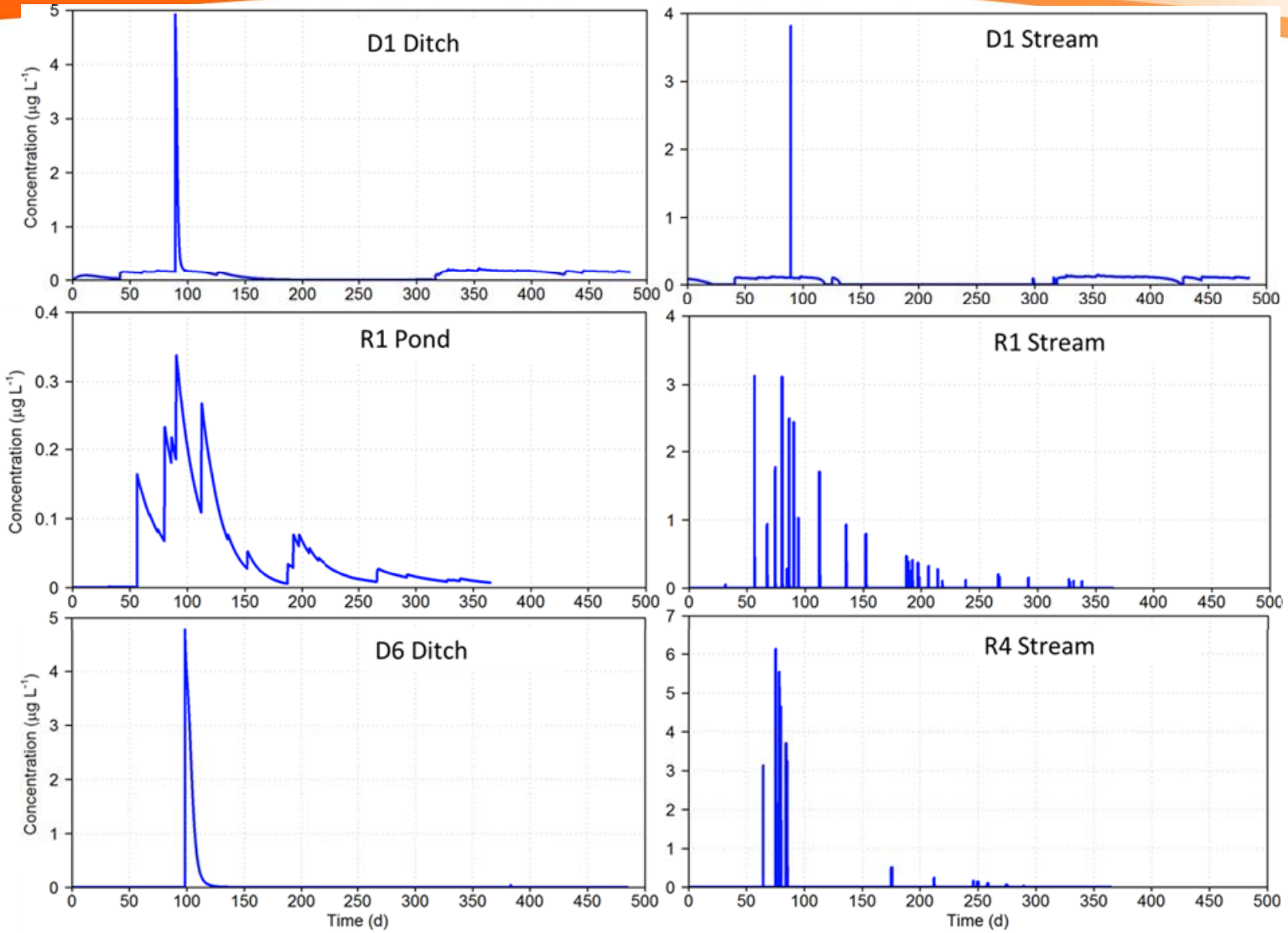
- Fungicides
- Tiered approach in effect assessment
- Linking exposure to effects

Practical examples

Fungicide F_A case study (Appendix H.2)

- Anilinopyrimidine
- Inhibitor of methionine biosynthesis
- Use in winter wheat
- 1 application in spring (0.75 kg/ha)
- FOCUS Step 3 calculations

Typical exposure profiles for F_A (FOCUS sw)



Step 3 $PEC_{sw;max}$: 0.163–5.050 µg/L

Tier 1 effect assessment

	Acute L(E)C_{50} (µg a.s./L)	Chronic EC_x/NOEC (µg a.s./L)
Americamysis bahia	18.2 (96 h)	-
Daphnia magna	33 (48 h)	7.5 (21 d NOEC)
Chironomus riparius	1 900 (48 h)	140 (28 d EC_{10})
Oncorhynchus mykiss	2 500 (96 h)	-
Pimephales promelas	-	485 (36 d NOEC)
Scenedesmus subspicatus	-	1200 (72 h E_rC_{50})

- AF of 100 to the lowest acute toxicity value (18.2 µg/L)

  Tier 1 $RAC_{sw;ac}$ = 0.185 µg/L
- AF of 10 to the lowest chronic toxicity value (7.5 µg/L).

  Tier 1 $RAC_{sw;ch}$ = 0.75 µg/L

Tier 2A effect assessment

	Acute L(E)C_{50} (µg a.s./L)	Chronic EC_{10}/NOEC	Taxonomy
Americamysis bahia	18.2		Crustacea
Daphnia magna	33	7.5 (repro)	Crustacea
Daphnia longispina	120		Crustacea
Ceriodaphnia dubia	150		Crustacea
Asellus aquaticus	210	12.1 (mort.)	Crustacea
Mesocyclops leuckarti	220		Crustacea
Halella azteca	980		Crustacea
Thamnocephalus plat.	1 100		Crustacea
Geomean Crustacea	**245.9**		
Chironomus riparius	1 900	140	Insecta
Chaoborus sp.	3 500		Insecta
Cloeon dipterum	3 850		Insecta
Crassostrea virginia	758		Bivalvia
Lymnaea stagnalis	2 900		Gastropoda
Scenedesmus subspicatus	4 600		Green alga
Pseudokirchneriella subcap.	1 200		Green alga
Navicula pelliculosa	3 760		Diatom
Anabaena flos-aquae	2 200		Blue-green alga
Lemna gibba	3 200		Vascular plant

Geom-$RAC_{sw;ac}$ of 2.459 µg/L (crustaceans and AF of 100)

Tier 2B effect assessment

SSD approach is possible on basis of acute toxicity data only

	N	Median HC5 (µg a.s./L)	LL HC5 (µg a.s./L)	Goodness-of-fit SSD curve
All taxa (incl. fish)	19	46.73	13.15	No
All taxa (excl. fish)	18	41.91	11.03	No
Invertebrates	**13**	**23.04**	**4.08**	**Yes**
Crustaceans	8	13.90	1.68	Yes

- SSD curve for invertebrates is selected
- AF of 3 – 6 has to be applied to median HC5

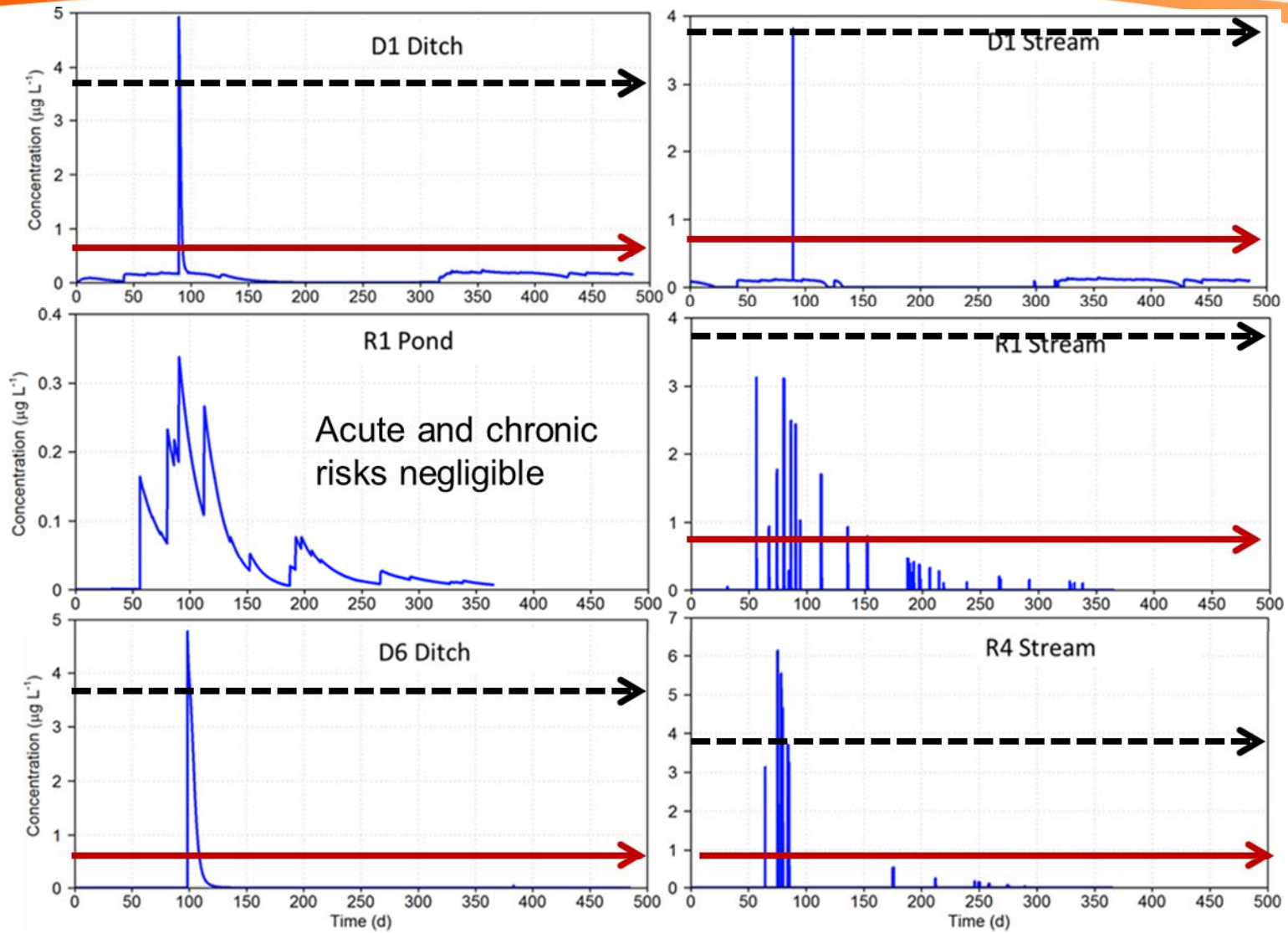
Tier 2B acute effect assessment

1. The lower limit value of the HC5 
2. Tier 1 & Tier 2A RACs not in conflict with AF 6 
3. Crustacean toxicity data in lower tail SSD 
4. Steepness of the SSD curve 
5. Chronic effects (Acute/chronic ratio >10) 

AF of 6 is selected

$SSD\text{-}RAC_{sw;ac}$ = 3.84 µg/L

Preliminary risk assessment (potential risks in most scenarios)



→ Tier 1 $RAC_{sw;ch}$ ⇢ Tier 2B $RAC_{sw;ac}$

Tier 3 effect assessment

- Lentic mesocosm study (GLP; R1-2)
- Repeated application (3x; weekly) of fungicide F_A (nominal 2.0 – 162 µg/L)
- Dissipation DT50 = 9-11 days (realistic to worst case exposure relative to field
- More than 8 taxa of potentially sensitive group (including 8 crustacean)
- See summary Table H.11 on page 246-247

ETO-RAC$_{sw;ac}$ & ETO-RAC$_{sw;ch}$ = 3.03 µg/L

(Effect class 2 and AF of 3; Ri-2 study)

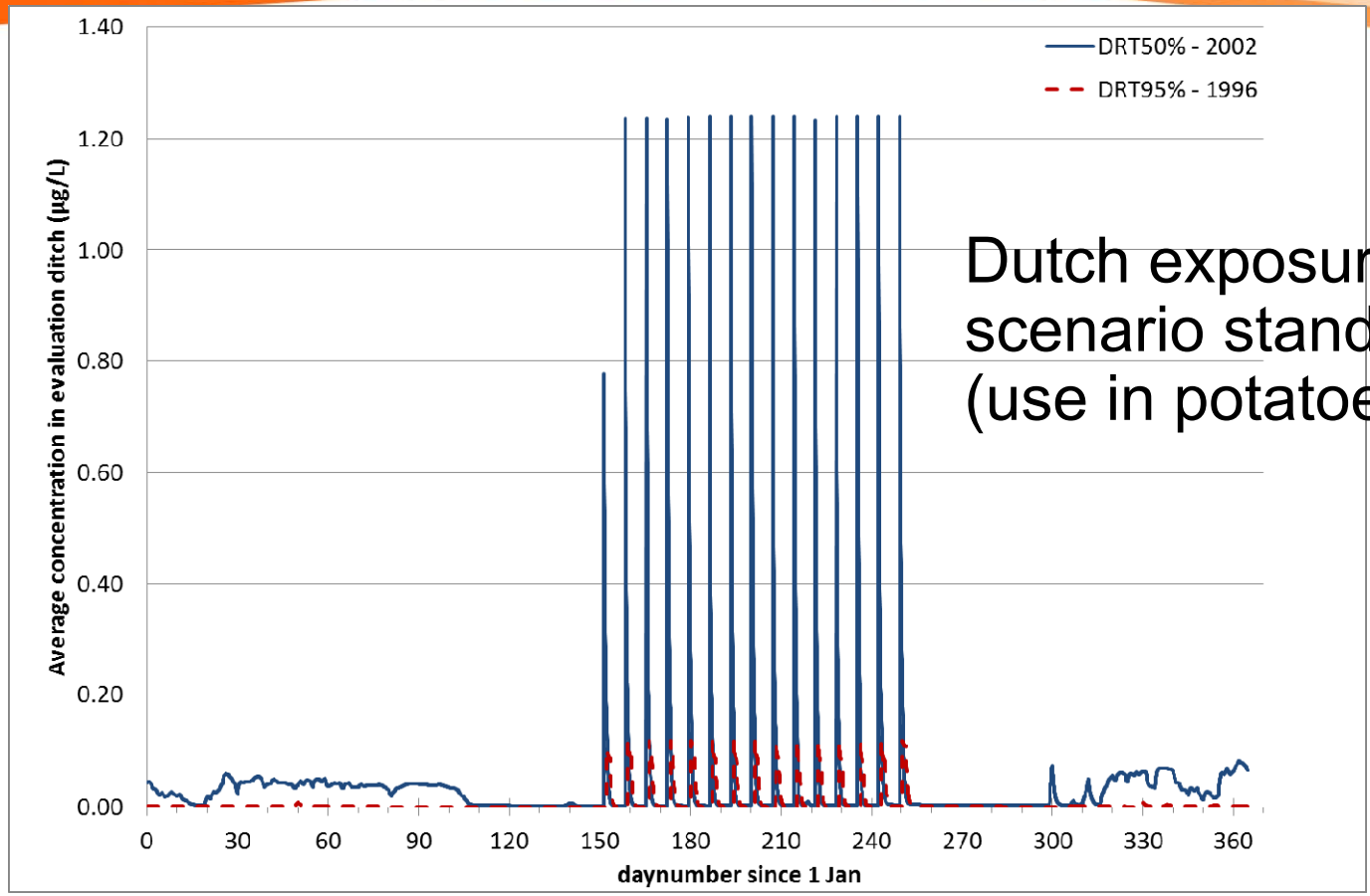
ERO-RAC$_{sw;ac}$ & ERO-RAC$_{sw;ch}$ = 5.90 µg/L

(Effect class 3A and AF of 4; Ri-2 study)

Summary F_A: Risks acceptable on basis of recovery option only

	Threshold option		Recovery option	
Scenario	**$PEC_{sw;max}$ (µg/L)**	**$ETO\text{-}RAC_{sw;ac}$ $ETO\text{-}RAC_{sw;ch}$ (µg/L)**	**$PEC_{sw;max}$ (µg/L)**	**$ERO\text{-}RAC_{sw;ac}$ $ERO\text{-}RAC_{sw;ch}$ (µg/L)**
D1 Ditch	5.050	3.030	5.050	5.090
D1 Stream	3.350	3.030	3.350	5.090
D2 Ditch	4.923	3.030	4.923	5.090
D2 Stream	4.345	3.030	4.345	5.090
D3 Ditch	4.740	3.030	4.740	5.090
D4 Pond	0.163	3.030	0.163	5.090
D4 Stream	3.692	3.030	3.692	5.090
D5 Pond	0.165	3.030	0.165	5.090
D5 Stream	3.256	3.030	3.256	5.090
D6 Ditch	4.654	3.030	4.654	5.090
R1 Pond	0.206	0.75 (Tier 1)	0.206	0.75 (Tier 1)
R1 Stream	3.124	3.030	3.124	5.090
R3 Stream	4.388	3.030	4.388	5.090
R4 Stream	3.124	3.030	3.124	5.090

Case study: Fungicide Fun_2



Dutch exposure scenario standard ditch (use in potatoes)

50% drift red.: PEC_{max}= 1.241 µg/L; $PEC_{7d\text{-}twa}$= 0.087 µg/L; $PEC_{7d\text{-}twa}$= 0.077 µg/L

95% drift red.: PEC_{max}= 0.118 µg/L ; $PEC_{7d\text{-}twa}$= 0.024 µg/L

Tier 1: Fun_2

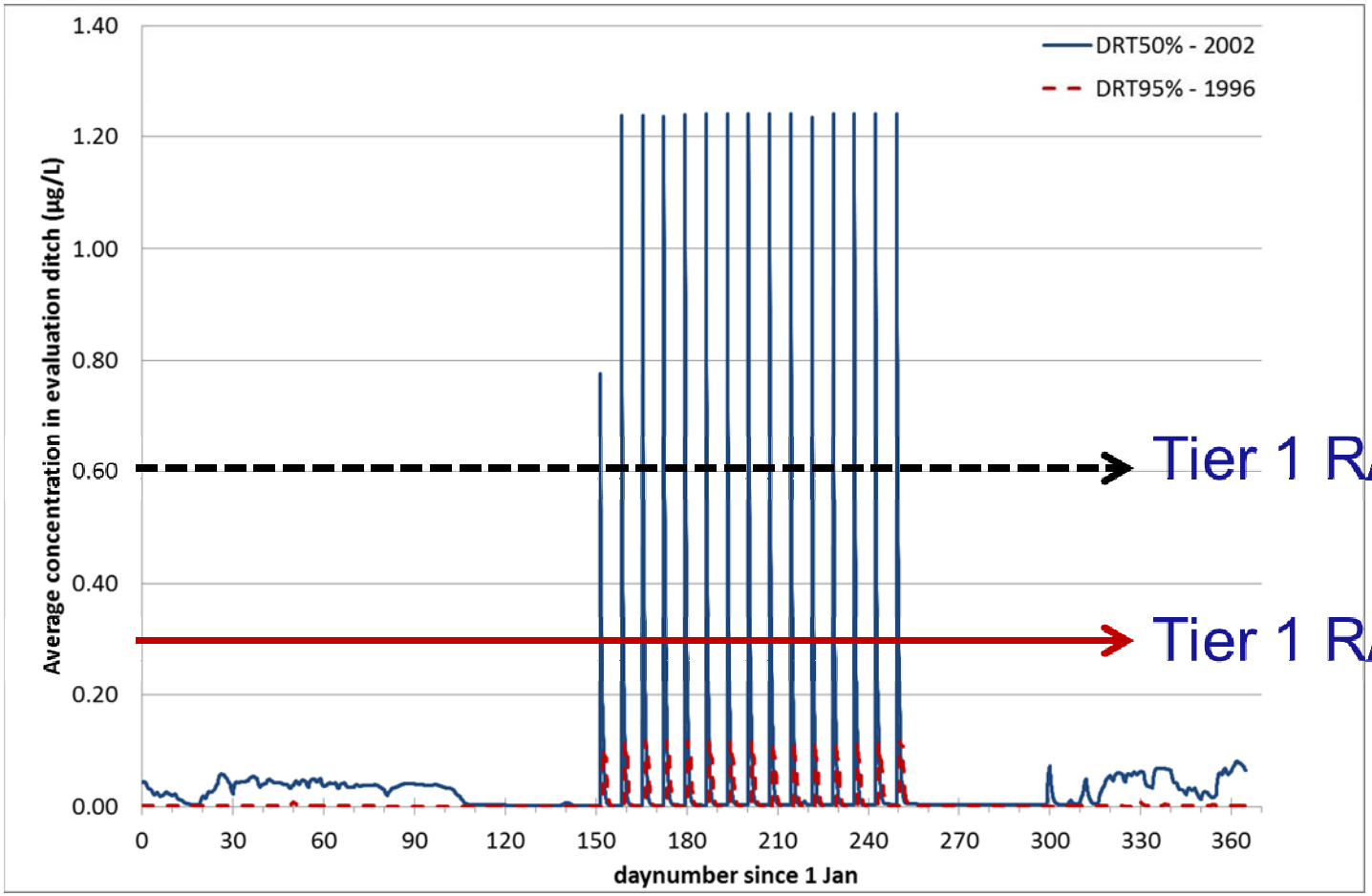
	Acute (µg/L)	Chronic (µg/L)
Daphnia magna	94 (48 h EC_{50})	8.5 (21 d NOEC)
Chironomus riparius	1995 (96 h LC_{50})	-
Oncorhynchus mykiss	63 (96 h LC_{50})	2.9 (98 d NOEC)
Scenedesmus subspicatus	-	1799 (72 h E_rC_{50})

- AF of 100 to the lowest acute toxicity value (63 µg/L)

  Tier 1 $RAC_{sw;ac}$ = 0.63 µg/L
- AF of 10 to the lowest chronic toxicity value (2.9 µg/L).

  Tier 1 $RAC_{sw;ch}$ = 0.29 µg/L

Preliminary risk assessment Fun_2



- Negligible risks for 95% drift reduction only

Tier 2 Effect assessment fish (Fun_2)

Fish	Acute LC_{50} (µg/L)	Chronic NOEC (µg/L)
Oncorhynchus mykiss	63	2.9 (growth)
Pimephales promelas	109	12.0 (growth)
Lepomis macrochirus	55	9.8 (growth)
Danio rerio	120	
Cyprinodon variegatus	89	
Cyprinus carpio	150	
Geomean	91.97 (AF of 100)	6.99 (AF of 10)
Geom-RAC_{sw}	**0.920**	**0.699**
Median HC_5	46.74 (AF of 9)	
SSD-RAC_{sw}	**5.19**	

$SSD\text{-}RAC_{sw;ac}$ > $PEC_{sw;max}$ (1.24 µg/L) → acute risk low

$Geom\text{-}RAC_{sw;ch}$ < $PEC_{sw;max}$ (1.24 µg/L) → potential chronic risk

$Geom\text{-}RAC_{sw;ch}$ > $PEC_{sw;7d\text{-}twa}$ (0.087 µg/L) → low chronic risk

(TWA approach according to criteria section 4.5.2 AGD)

Is higher tier RAC for fish and Fun_2 protective for non-vertebrates?

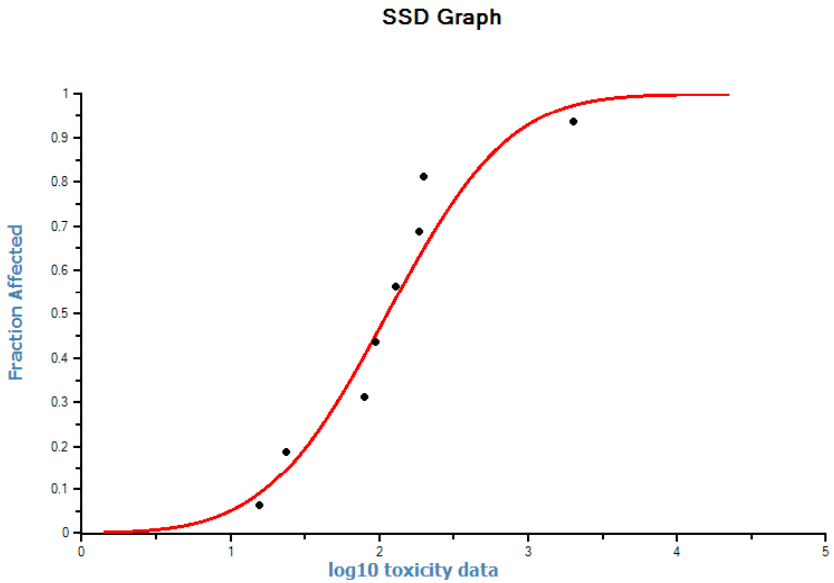
	Acute (µg/L)	Chronic (µg/L)
Higher tier RAC fish	**5.19 (SSD-RAC)**	**0.699 (Geom-RAC)**
Daphnia magna	94 (48 h EC_{50}) 0.94 (Tier 1 RAC)	8.5 (21 d NOEC) 0.85 (Tier 1 RAC)
Scenedesmus subspicatus	-	1799 (72 h E_rC_{50}) 179.9 (Tier 1 RAC)

- Potential acute risks for invertebrates (not covered by SSD-RAC of 5.19 µg/L for fish and $PEC_{sw;max}$ of 1.24 µg/L)

	Taxonomic group	Acute L(E)C_{50} (µg/L)
Daphnia magna	Crustacea	94
Gammarus pulex	Crustacea	79.1
Asellus aquaticus	Crustacea	129,4
Chironomus riparius	Insecta	1995
Cloeon dipterum	Insecta	198.4
Lymnaea stagnalis	Mollusca	185.1
Dugesia lugubris	Turbellaria	23.8
Lumbriculus variegatus	Oligochaeta	15.7

- Toxicity data for 5 different taxonomical groups
- Geomean approach less applicable (for several taxonomical groups 1 species tested only)
- SSD approach possible (8 taxa tested)

Tier 2B for invertebrates (FUN_2)



- Median HC_5 = 8.889 µg/L; LL HC_5 = 1.013 µg/L
- AF of 3 – 6 has to be applied to median HC_5
- $SSD\text{-}RAC_{sw;ac}$= 1.482 – 2.963 µg/L
- $SSD\text{-}RAC_{sw;ac}$> $PEC_{sw;max}$ (1.24 µg/L)

  → acute risk acceptable for invertebrates

Risk due to secondary poisoning (FUN_2)

- Log P_{OW} = 4
- BCF = 1023
- $NOAEL_{bird}$ = 500 mg/kg_{diet}
- $NOAEL_{mammel}$ = 10 mg/kg_{diet}

$$RAC_{SP} = \frac{NOAEL_{bird}}{5 \cdot 0.159 \cdot BCF_{fish} \cdot BMF} \text{ or } \frac{NOAEL_{mammal}}{5 \cdot 0.138 \cdot BCF_{fish} \cdot BMF}$$

→ RAC_{sp} = 615 µg/L (bird) or 14 µg/L (mammal)

→ RAC_{sp} of 14 µg/L > $PEC_{sw;21d\text{-}twa}$ of 0.077 µg/L

(low risks due to secondary poisoning for 50% drift reduction exposure scenario)

European Food Safety Authority

Thank you !