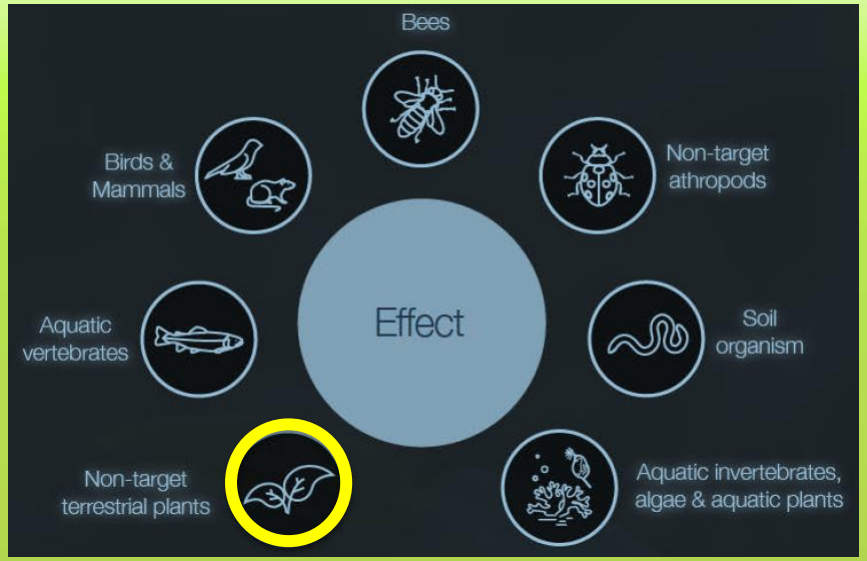
Risk assessment on Non-target terrestrial plants (NTTP) in the EU



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Realisation:
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Overview

- Regulations & data requirements (European Union)
- Guidance document & testing guidelines
- Basic study types & related endpoints
- Higher tier studies
- Virtual Standard Risk Assessment Example
- Potential refinement options

Regulations & data requirements (EU)

Regulation (EC) No. 1107/2009 concerning the placing of plant protection products on the market

& corresponding regulations:

- Regulation (EU) No. 283/2013
  = data requirements for active substances
- Regulation (EU) No. 284/2013
  = data requirements for plant protection products
- Regulation (EU) No. 546/2011
  = Uniform Principles

Most important documents for NTTP

- Guidance Document on Terrestrial Ecotoxicology, SANCO/10329/2002, rev. 2 final, 17.10.2002

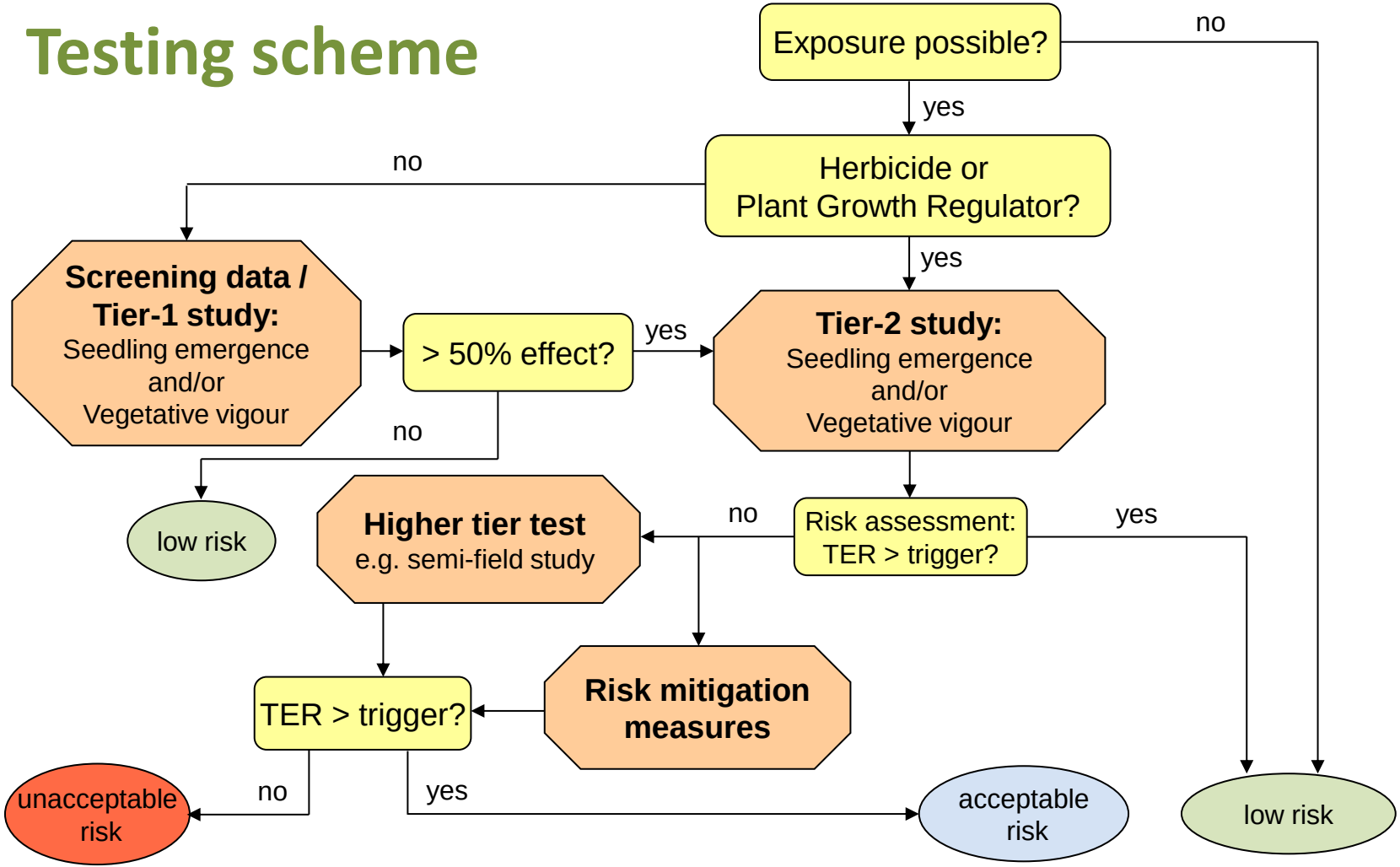
- Guidelines relevant for NTTP testing
  - OECD TG 208, 2006 (SE) (& US-EPA: OCSPP 850.4100)
  - OECD TG 227, 2006 (VV) (& US-EPA: OCSPP 850.4150)

- EFSA Scientific Opinion on NTTP (EFSA Journal 2014:12(7):3800);
  non-binding precursor to a new Guidance Document

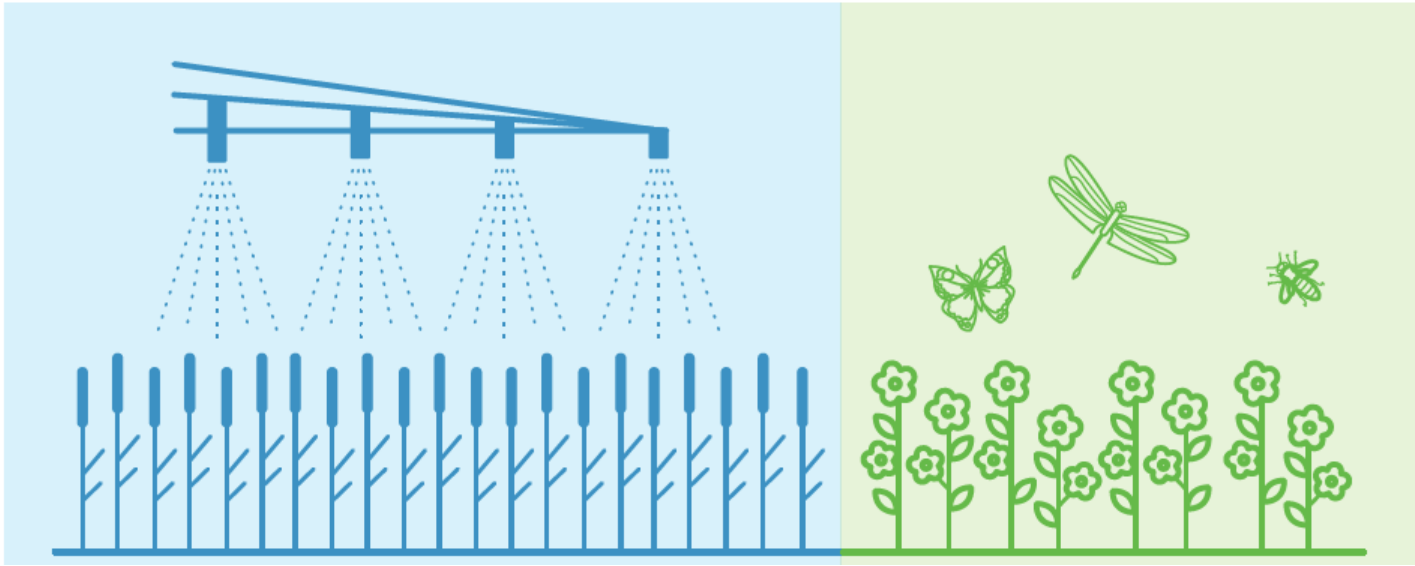
Terms & Abbreviations

Term	Explanation
DRN	Drift reducing nozzles
Effect measurements	In the context of NTTP studies effects are commonly measured for the following endpoints: emergence, survival, fresh/dry weight (and length) of the shoot, growth and symptoms of phytotoxicity
Effect value	Dependent from study design & underlying guideline, effect values (often also referred to as 'endpoints') have different names (abbreviations) as they signify different effect levels that have been measured or calculated. Examples: ER_{50}, NOER etc.
ER_{50}	Effect rate at which the tested species shows an effect at the 50% level
ER_{25}	Effect rate at which the tested species shows an effect at the 25% level
HR_5 / HC_5	Hazard Rate / Concentration below which less than 5% of species will be adversely affected
LOER	Lowest Observed Effect Rate
NOER	No Observed Effect Rate
NTTP	Non-target terrestrial plants
PER	Predicted Environmental Rate
prod.	Product, i.e. formulated product
SE	Seedling Emergence
SSD	Species Sensitivity Distribution
TER	Toxicity to Exposure Ratio (= calculated for risk assessment)
VV	Vegetative Vigour

Testing scheme



Terrestrial “non-target plants are non-crop plants located outside the treatment area”* - i.e. outside the field



In-field Off-field

* See ‚Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC’, SANCO/10329/2002 rev 2 final, 2002; p. 31

Study types

- Seedling Emergence and Growth (OECD TG 208) = SE
- Vegetative Vigour (OECD TG 227) = VV

Depending on the expected herbicidal properties of the product these 2 study types can be conducted in the greenhouse / growth chamber as:

- ➢ Tier-1 study: limit test = **single** rate test
- ➢ Tier-2 study: rate-response test = **multiple** rate test

In case strong effects are observed under worst-case greenhouse conditions, additional studies under more realistic conditions might be performed to determine if mitigation will be needed when the product is used on the field:

- ➢ Higher tier study: e.g. semi-field or field testing; currently no guidance available

Test species

Crop species are usually selected as test species, because

- They are easy to obtain in good quality (healthy test organisms) and relatively easy to maintain.
- They provide good homogeneity - thus providing higher reproducibility, statistical power and enabling the detection of minor effects (i.e. high sensitivity of the test system).
- They cover a wide range of plant families (Poaceae, Brassicaceae, Chenopodiaceae, Compositae, Cucurbitaceae, Leguminosae, Linaceae, Polygonaceae, Solanaceae, Umbelliferae, Alliaceae).
- Can be tested globally without plant health and importation issues.

Tier-1: Limit test or initial screening data

- At least 6 plant species from as many families as possible (monocots and dicots)
- Tested at highest nominal application rate or predicted exposure rate
- Seedling emergence (OECD TG 208) and/or Vegetative vigour (OECD TG 227)

⇒ Detection of potentially sensitive species

Tier-1 studies are mostly done for Fungicides or Insecticides without herbicidal properties

Relevant adverse effect level: 50% → ER_{50}

Tier-2: Rate-response testing

- 6-10 plant species from as many families as possible (monocots and dicots)
- Rate-response test, based on geometric series of test rates that allows statistical calculation of a rate-response curve
- Seedling emergence (OECD TG 208) and/or Vegetative vigour (OECD TG 227)

Tier-2 studies are mostly done for Herbicides or products with herbicidal properties

Relevant adverse effect level: 50% → ER_{50}

Seedling Emergence & Growth test

OECD TG 208 (US: OCSPP 850.4100)

Aim = assess potential effects on seedling emergence and early growth of plants

- Application of test substance:
  a) Surface application: seeds are sown in soil, test item is sprayed onto soil surface
  b) Incorporation into soil (in special cases): test item is mixed with soil; seeds are sown in soil
- Evaluation of effects usually after 14-21 days,
  after 50% of seedlings in the control have emerged
- Treatment groups: test item rate(s), control
- Regular recordings: emergence, visual phytotoxicity, survival

<u>Endpoints</u>

- seedling emergence
- survival
- shoot dry weight
- shoot height, if required by regulatory authorities
- visual detrimental effects on different parts of the plants and growth stages

Vegetative Vigour test

OECD TG 227 (US: OCSPP 850.4150)

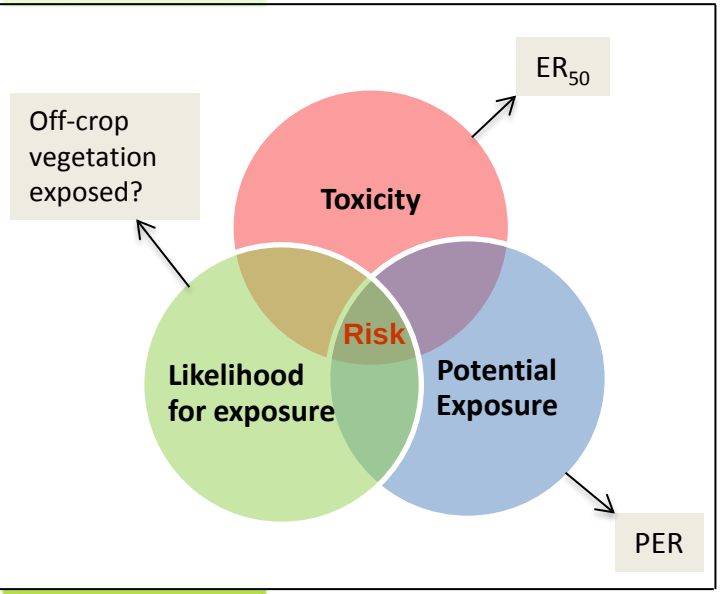
Aim = assess potential effects on plants following deposition on leaves and above-ground portions of young plants

- Test item is sprayed onto potted seedlings when they are at the 2- to 4- true leaf stage
- Evaluation of effects 21-28 days after treatment
- Treatment groups: test item rate(s), control
- Regular recordings: visual phytotoxicity and survival

Endpoints

- survival
- shoot dry weight
- shoot height, if required by regulatory authorities
- visual detrimental effects on different parts of the plants and growth stages

General principles – Toxicity / Exposure



TER = **T**oxicity to **E**xposure **R**atio

where

Toxicity → Endpoint value from a study (i.e. ER_{50})

Exposure → $PER_{off\text{-}field}$ - Predicted Environmental Rate

$$TER = \frac{\text{toxicity value } (ER_{50})}{\text{exposure } (PER_{off-field})}$$

→ Low risk to non-target terrestrial plants is indicated if TER ≥ 5 (deterministic approach)
(see Uniform Principles as laid down in Reg. (EU) No 546/2011)

Risk assessment options

Testing and risk assessment is conducted with the formulated product

$$\mathrm{TER} = \frac{\text{toxicity value } (\mathrm{ER}_{50 \text{ or}}\, \mathrm{HR}_5)}{\text{exposure } (\mathrm{PER}_{\mathrm{off-field}})}$$

A - Deterministic approach

- Toxicity to Exposure Ratio (TER) based on overall lowest ER_{50} (most sensitive species)
- If TER ≥ 5 → acceptable risk

B - Probabilistic approach

- Toxicity to Exposure ratio (TER) based on HR_5 (Hazard Rate at which less than 5% of species are adversely affected) → considers the range of sensitivities in the species tested
- If TER ≥ 1 → acceptable risk

Risk assessment

Example: Herbicide

The following example is based on a virtual product containing three virtual active substances (X, Y and Z) and a virtual intended use pattern.

Formulated product: (Herbicide)	**X+Y+Z SC 650** (400 g X/L + 100 g Y/L + 150 g Z/L)
Intended use pattern	1 x 1.0 L prod./ha, maize (BBCH 10)

Virtual endpoints (product)

Endpoints and effect values relevant for the risk assessment for non-target terrestrial plants

Species	Substance	Exposure System	Results	Reference
Beta vulgaris $_d$ [1)] *Brassica napus* $_d$ [2)] *Brassica oleracea* $_d$ [3)] *Cucumis sativus* $_d$ [4)] *Glycine max* $_d$ [5)] *Lycopersicum esculentum* $_d$ [6)] *Allium cepa* $_m$ [7)] *Hordeum vulgare* $_m$ [8)] *Triticum aestivum* $_m$ [9)] *Zea mays* $_m$ [10)]	X+Y+Z SC 650	21 d Seedling emergence Tier 2	1) ER_{50} dw = 150 mL/ha 2) ER_{50} dw = 175 mL/ha 3) ER_{50} dw = 180 mL/ha 4) ER_{50} dw = 225 mL/ha 5) ER_{50} dw = 200 mL/ha 6) ER_{50} dw = 175 mL/ha 7) ER_{50} dw = 185 mL/ha 8) ER_{50} dw > 250 mL/ha 9) ER_{50} dw = 190 mL/ha 10) ER_{50} dw = 160 mL/ha	Appendix 2 Smith, 2010 & additional calculations
			HR_5 = 118.5 mL/ha	
Beta vulgaris $_d$ [1)] *Brassica napus* $_d$ [2)] *Brassica oleracea* $_d$ [3)] *Cucumis sativus* $_d$ [4)] *Glycine max* $_d$ [5)] *Lycopersicum esculentum* $_d$ [6)] *Allium cepa* $_m$ [7)] *Hordeum vulgare* $_m$ [8)] *Triticum aestivum* $_m$ [9)] *Zea mays* $_m$ [10)]	X+Y+Z SC 650	21 d Vegetative vigour Tier 2	1) ER_{50} dw = 25.5 mL/ha 2) ER_{50} dw = 50 mL/ha 3) ER_{50} dw = 120 mL/ha 4) ER_{50} dw > 100 mL/ha 5) ER_{50} dw = 90 mL/ha 6) ER_{50} dw = 100 mL/ha 7) ER_{50} dw = 75 mL/ha 8) ER_{50} dw > 100 mL/ha 9) ER_{50} dw = 70 mL/ha 10) ER_{50} dw = 55 mL/ha	Appendix 2 Smith, 2011 & additional calculations
			HR_5 = 28.9 mL/ha	

m: monocotyledonous; d: dicotyledonous

HR_5 can be calculated, if at least 6 acceptable ER_{50} values are available

Overall lowest endpoints

A - Deterministic approach

a) Calculate **PER** off-field (Predicted Environmental Rate):

Single appl. rate [mL*/ha] × MAF × Drift rate = $PER_{off\text{-}field}$ [mL*/ha]

b) Calculate **TER** (based on lowest ER_{50}):

ER_{50} [mL*/ha] / $PER_{off\text{-}field}$ [mL*/ha] = TER

Trigger:
TER ≥ **5**

* or [g prod./ha]

Exposure assessment

Spray drift = **key exposure route** for terrestrial plants located in the vicinity of the treated area

Basic drift values for **one application** (Rautmann et al., 2001) – example „field crops“

Basic drift values for one application **Ground sediment [%] of the application rate (90th percentiles)**								
Distance	Field crops	Fruit crops		Grapevine		Hops	Vegetables Ornamentals Small fruits	
[m]		early	late	early	late		Height < 50 cm	Height > 50 cm
1	2.77						2.77	
3		29.20	15.73	2.70	8.02	19.33		8.02
5	0.57	19.89	8.41	1.18	3.62	11.57	0.57	3.62
10	0.29	11.81	3.60	0.39	1.23	5.77	0.29	1.23

Deterministic approach - Example

Intended use	Spray application, Maize (BBCH 10)			
Active substance/product	X + Y + Z SC 650 (virtual product)			
Application rate (mL prod./ha)	1 × 1000			
MAF	1 (single application)			
Test species	**ER_{50} (mL/ha)**	**Drift rate (%)**	**$PER_{off\text{-}field}$ (mL/ha)**	**TER criterion: TER ≥ 5**
Beta vulgaris Vegetative vigour	25.5	2.77	27.7	**0.9**
Beta vulgaris Seedling emergence	150	2.77	27.7	5.4

Values in bold breach the trigger

The resulting TER for Seedling Emergence is above the trigger

→ No further risk assessment required.

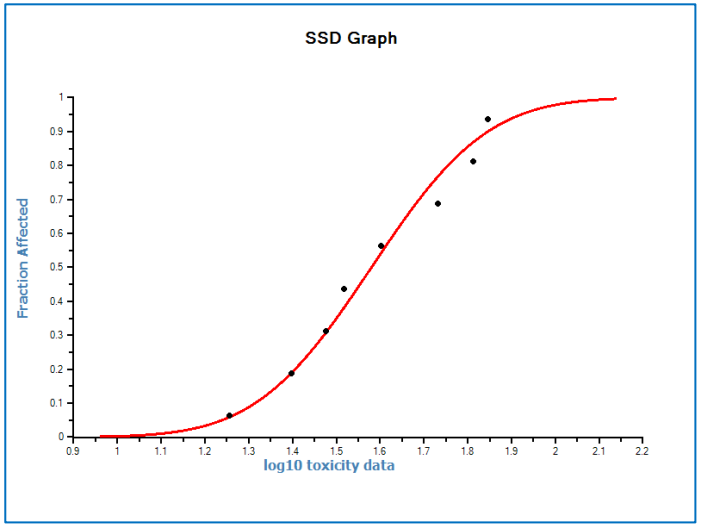
The resulting TER for Vegetative Vigour is below the trigger of 5

→ **Refinement of the risk assessment required**

B - Probabilistic approach

Species Sensitivity Distribution (SSD)

- Minimum of 6 species (with adequately usable endpoints)
- Calculation of a **HR_5** (hazard rate at which less than 5% of species are adversely affected)
- Risk assessment with HR_5 (instead of ER_{50})
- Trigger = 1

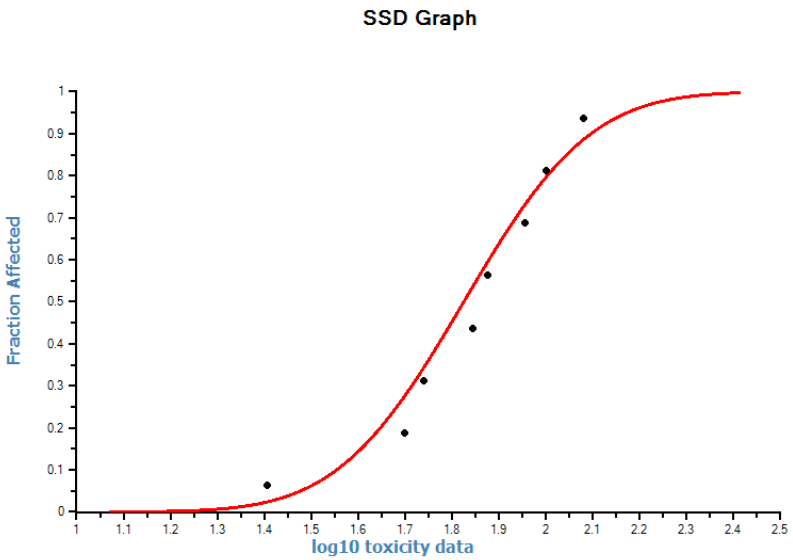


Example SSD - graph

B – Example HR_5 calculation for virtual product

Calculations performed for virtual VV endpoints (n=8) based on software ETX*

SSD graph – VV endpoints (n=8)



HR_5 results			
Name	**Value**	**log10(Value)**	**Description**
LL HR5	14.15638	1.150952151	lower estimate of the HR5
HR5	28.93972	1.461494299	median estimate of the HR5
UL HR5	41.91294	1.622348133	upper estimate of the HR5
sprHR5	2.960711	0.471395983	spread of the HR5 estimate

Median **HR_5 = 28.9 mL prod./ha**

Goodness of fit toxdata (for virtual example):

Anderson-Darling test for normality				
Sign. level	Critical	Normal?		
0.1	0.631	Accepted		
0.05	0.752	Accepted	AD Statistic:	0.303206
0.025	0.873	Accepted	n:	8
0.01	1.035	Accepted		
Kolmogorov-Smirnov test for normality				
Sign. level	Critical	Normal?		
0.1	0.819	Accepted		
0.05	0.895	Accepted	KS Statistic:	0.508352
0.025	0.995	Accepted	n:	8
0.01	1.035	Accepted		
Cramer von Mises test for normality				
Sign. level	Critical	Normal?		
0.1	0.104	Accepted		
0.05	0.126	Accepted	CM Statistic:	0.027753
0.025	0.148	Accepted	n:	8
0.01	0.179	Accepted		

* Source: RIVM, NL https://www.rivm.nl/rvs/Risicobeoordeling/Modellen_voor_risicobeoordeling/ETX

B - Probabilistic approach

a) Calculate **PER** off-field (Predicted Environmental Rate):

Single appl. rate [mL*/ha] × MAF × Drift rate = $PER_{off\text{-}field}$ [mL*/ha]

b) Calculate **TER** (based on HR_5):

HR_5 [mL*/ha] / $PER_{off\text{-}field}$ [mL*/ha] = TER

Trigger:
TER ≥ **1**

* or [g prod./ha]

Exposure assessment

Spray drift = **key exposure route** for terrestrial plants located in the vicinity of the treated area

Basic drift values for **one application** (Rautmann *et al.*, 2001) – example „field crops“

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[m]		early	late	early	late		Height < 50 cm	Height > 50 cm
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5	0.57	19.89	8.41	1.18	3.62	11.57	0.57	3.62
10	0.29	11.81	3.60	0.39	1.23	5.77	0.29	1.23

B - Probabilistic approach – Example

Intended use	Spray application, Maize (BBCH 10)			
Active substance/product	X + Y + Z SC 650 (virtual product)			
Application rate (mL prod./ha)	1 × 1000			
MAF	1 (single application)			
Test species	**HR_5 (mL/ha)**	**Drift rate (%)**	**$PER_{off\text{-}field}$ (mL/ha)**	**TER criterion: TER ≥ 1**
Vegetative vigour (8 species)	28.9	2.77	27.7	1.04

The resulting TER for Vegetative Vigour is above the trigger

→ No further risk assessment required.

Refinement / Risk mitigation measures

- **Higher tier risk assessment** based on semi-field data
- **Buffer zones** to sensitive areas (5m, 10m etc.)
- **Drift reducing application techniques**
  i.e. DRN/DRT (drift reducing nozzles/technology)
  drift reduction by 50%, 75% and 90%

➢ **Mitigation measures are highly specific and depend on member state requirements**

Exposure assessment – in-crop buffer zones

Basic drift values for **one application** (Rautmann et al., 2001) – example „field crops“

Basic drift values for one application
Ground sediment [%] of the application rate (90th percentiles)

Distance	Field crops	Fruit crops		Grapevine		Hops	Vegetables Ornamentals Small fruits	
[m]		early	late	early	late		Height < 50 cm	Height > 50 cm
1	2.77						2.77	
3		29.20	15.73	2.70	8.02	19.33		8.02
5	0.57	19.89	8.41	1.18	3.62	11.57	0.57	3.62
10	0.29	11.81	3.60	0.39	1.23	5.77	0.29	1.23

Buffer

Deterministic approach – Refinement example

Refined assessment for the risk on non-target plants after use of X+Y+Z SC 650 on maize

Intended use		Spray application on maize			
Active substance/product		X + Y + Z SC 650 (virtual product)			
Application rate (mL/ha)		1 × 1000			
MAF		1			
Buffer strip (m)	**Drift rate**	**$PER_{off\text{-}field}$ (mL/ha)**	**$PER_{off\text{-}field}$ 50 % drift red. (mL/ha)**	**$PER_{off\text{-}field}$ 75 % drift red. (mL/ha)**	**$PER_{off\text{-}field}$ 90 % drift red. (mL/ha)**
1	0.0277	27.7	13.85	6.93	2.77
5	0.0057	5.7	2.85	1.43	0.57
10	0.0029	2.9	1.45	0.73	0.29
Toxicity value		**TER**			
ER_{50} = 25.5 mL/ha (VV)		**criterion: TER ≥ 5**			
1		**0.9**	**1.8**	**3.7**	9.2
5		**4.5**	8.9	17.9	44.7
10		8.8	17.6	35.2	87.9

MAF: Multiple application factor; PER: Predicted environmental rate; TER: toxicity to exposure ratio. TER values shown in bold fall below the relevant trigger.

RMM: 10 m buffer without drift reduction
Altern.: 5m buffer & 50% drift reducing nozzles (DRN) or 90% DRN without buffer

Conclusion of the NTTP risk assessment example

Conclusion:

The deterministic risk assessment for product X+Y+Z SC 650 resulted in a TER above the trigger based on the lowest SE endpoint. Risk mitigation measures are required to pass the trigger for the lowest VV endpoint.

Proposed risk mitigation measures would be:

- 10 m buffer without drift reduction or
- 5 m buffer & 50% drift reducing nozzles (DRN)
- or 90% DRN without buffer

The probabilistic risk assessment for product X+Y+Z SC 650 resulted in a TER above the trigger based on the HR_5 derived from vegetative vigour studies (n=8). No buffer or drift reduction technology needs to be applied.

Ultimately, no risk mitigation measures are required on the label.

Conditions for product submission and approval

- The applicant only submits a dossier for registration of a plant protection product, when Environmental Risk Assessment (ERA) showed acceptable risk for all assessment areas

- Authorities review the submitted dossier (containing study reports, evaluation and risk assessments + any further required data)
- Authorities grant registration/approval only if they agree on an acceptable risk for all assessment areas

→ Special mandatory conditions for use might apply (i.e. risk mitigation measures) which are printed on the label of the plant protection product