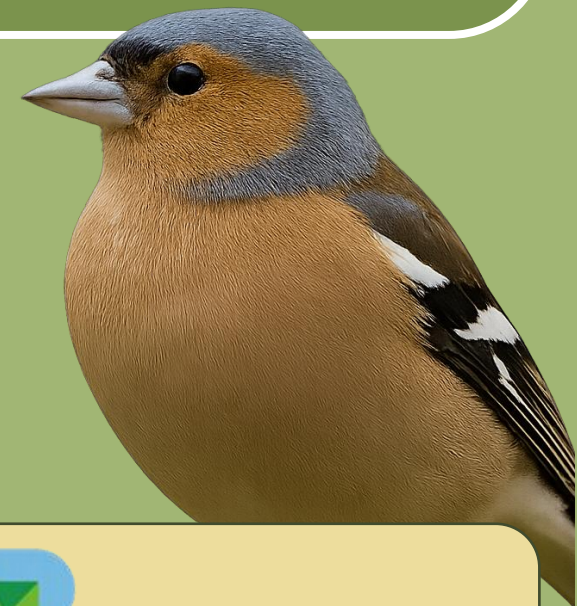
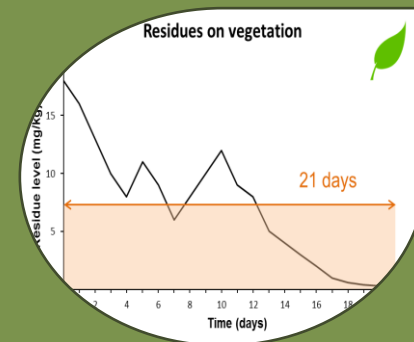


3rd Virtual Workshop on the revised EFSA Birds and Mammals Guidance Document

Background, Regulatory hurdles, Ambiguities, Lines of evidence,
Modelling - How best to approach the new fTWA assessment.

Jens Schabacker - RIFCON

Topic 1a: Background



RIFCON



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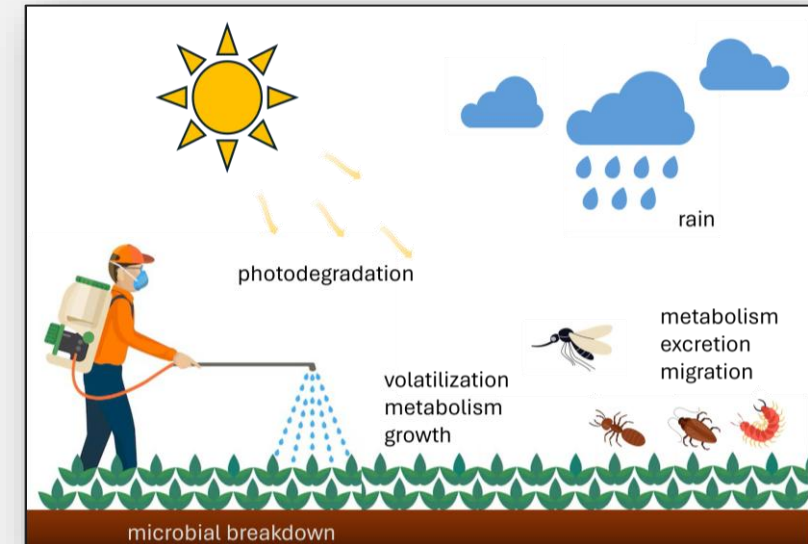
Background

GD Risk assessment for Birds and Mammals (EFSA 2023)

Chapter 6.1.4. Criteria to assess whether a time-weighted average factor can be used in the reproductive exposure assessment.

$$\text{Reproductive DDD} = \text{FIR} \times \sum_i (\text{AR} \times \text{RUD}_i \times \text{MAF}_{\text{repro},i} \times \text{fTWA}_i) / \text{bw}$$

- How should the degradation of a substance be taken into account when calculating exposure for reproductive assessments?



1 Residue decline

Pesticide residues decline due to:

- **Plants:** photodegradation, microbial breakdown, volatilization, metabolism, plant growth...
- **Arthropods:** metabolism, excretion, molting, death, migration...

$$C_t = C_0 e^{-kt}$$

where:

C(t): concentration at time t

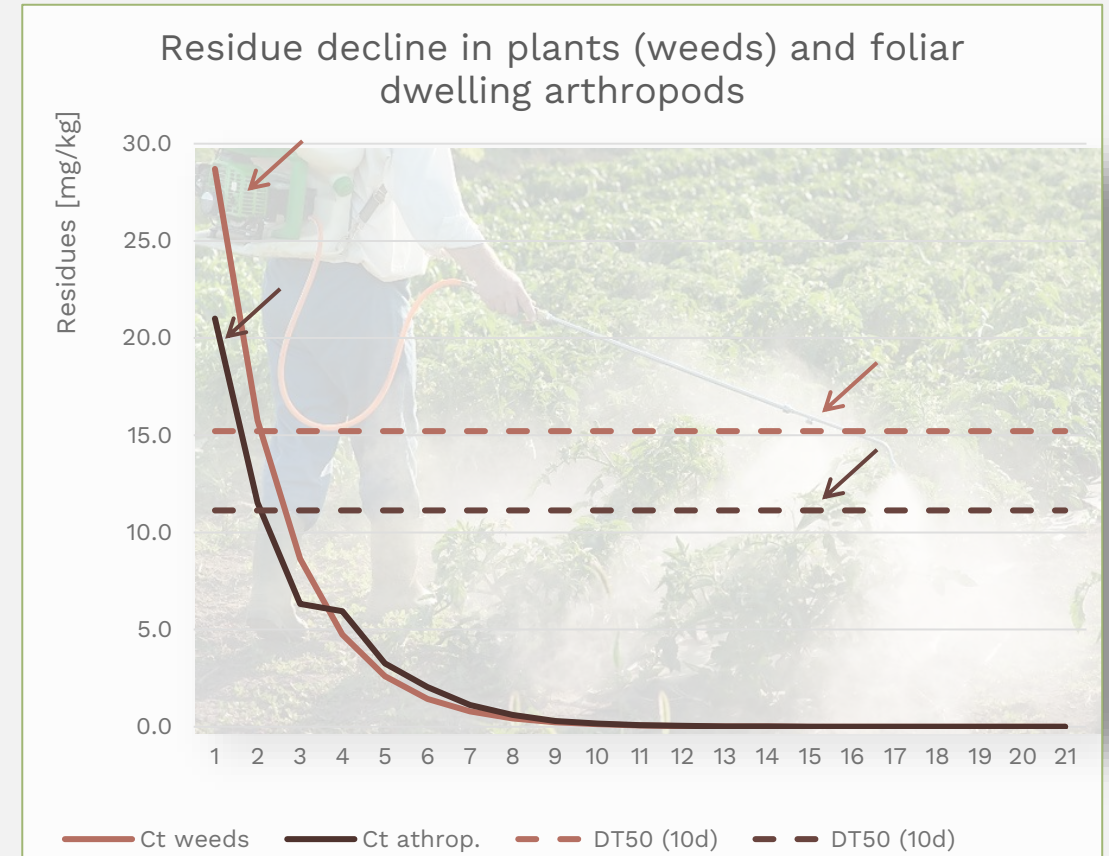
C₀: initial concentration

k: degradation rate constant, where $k = \ln_2 / DT_{50}$

$$fTWA = \frac{(1 - e^{(-kj)})}{kj}$$

For screening and Tier 1 assessments

$Dt_{50} = 10 \text{ d} \Rightarrow f_{TWA} = 0.53$ for all food items



“A constant exposure level [...] will have more serious long-term effects than an exposure pattern which starts with the same level and then rapidly declines, either due to accumulation of the substance [...] or due to accumulation of effects.” (Appendix H, EFSA 2023)

2 Sensitive life stage

Concern:

It is often unclear whether toxicity is due to

- prolonged exposure or
- exposure during a critical/sensitive life stage.
- **Developmental defects**
- **Reproductive effects** => e.g. abortion or embryonic mortality, eggshell thickness, number of offspring.
- **Sublethal effects on reproductive behavior** (Wildlife)
 - Mammals: effects on parental care during lactation and weaning, until the young become independent.
 - Birds: effects on pair formation and breeding site selection, incubation, parental care of nestlings and survival of fledgling birds.

Period of dividing zygote, implantation	Embryonic period (in weeks)								Fetal period (in weeks)—full term			
	1	2	3	4	5	6	7	8	9	16	20-36	38
Usually not susceptible to teratogens			Central nervous		• Indicates common site of action of teratogen							



3 Concern is not new!

This concern is not new:

- EFSA 2009, fTWA was used by default unless there was evidence showing that effects were due to short-term exposure.

However:

- The EFSA already held a discussion on the duration of exposure required to achieve an effect in 2009.
 - STE => ftwa = 1
 - LTE => ftwa = 0.53
- “It is intended to develop further guidance on criteria for determining which effects could be caused by short-term exposures” (EFSA 2009)
- Given in Chapter 6.1.4 (EFSA 2023)

4. | RISK ASSESSMENT MODULES FOR SPRAY APPLICATIONS

Step 3

Identify the appropriate indicator species and shortcut value for the crop under assessment from Table 10. If multiple applications are to be made, then Table 11 should be consulted and the appropriate 'multiple application factor' (MAF_m) should be used. Calculate the daily dietary dose (DDD):

$$DDD = \text{application rate} \times \text{shortcut value} \times TWA \times MAF_m$$

The value to be used for the time-weighted average factor (TWA) depends on whether the toxicity endpoint from Step 2 could be caused by a short-term exposure (STE) or only by a long-term exposure (LTE)²³.

- If the toxic effect is considered to be caused by LTE, use $TWA = 0.53$ (estimates time-weighted exposure over 21 days, assuming a default DT_{50} of 10 days).
- If the toxic effect is considered to be caused by STE, use $TWA = 1$ (one day exposure).

²³ It is intended to develop further guidance on criteria for determining which effects could be caused by short-term exposures. The Joint Working Group decided that, until such guidance is available, it should be assumed as a default that the effects are caused by LTE, unless there is specific evidence for the pesticide under assessment that the effect could be caused by STE.

EFSA Journal 2009; 7(12):1438 34/139

6.1.4. Criteria to assess whether a time-weighted average factor (fTWA) can be used in the reproductive exposure assessment

In the exposure calculation for reproductive assessments, it may be possible to take in to account the degradation of a substance in the form of a time-weighted average factor (fTWA). The use of an fTWA in the exposure calculations for the reproductive risk assessment assumes that the toxicity follows the rule of linear reciprocity because of continuous or variable exposure over an extended period of time (in this case 21 days, see Appendix H for discussions on the selected averaging period).

³² <https://r4eu.efsa.europa.eu/app/birds-mammals>

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However:

- The EFSA already held a discussion on the duration

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4 fTWA applicability check

1. Identify the ecologically relevant endpoint, (EFSA conclusion, endpoint refinement).
2. What is the endpoint based on?
 - Short-term or long-term toxic effect?
 - Is it the highest dose in a NOEL study?

- Toxicity tests often cannot distinguish between short-term and long-term effects.
- There is no clear definition of short-term and long term in terms of duration
- Data on mammal toxicity is more extensive than for birds.

Birds	OECD Nr.	Exposure	Reproductive parameters
Acute toxicity test	223	1 day	No
Short-term dietary toxicity	205	5 days	No
Sub-chronic and reproductive toxicity	206	20 weeks	Yes

Mammals	OECD Nr.	Exposure	Reproductive parameters
Acute toxicity	420, 423, 425	1 day	No
28-day toxicity study	407	28 d	No
90-day toxicity study (rodents/nonrodents)	408, 409	90 d	No
Carcinogenicity studies (rats/mice)	451, 452, 453	18 - 24 m	No
Reproductive studies with rodents (rats)	416, 443	2 Gen	Yes
Developmental studies with mammals (rats/rabbits)	414	Rat: 14/15 d Rabbit: 21/24 d	Yes
Neurotoxicity studies (rodents)	424, 426	-	Yes (OECD 426)

=> The GD is asking for information that the studies are not designed to provide.

4 fTWA applicability check

5.2.6. Selection of the endpoint for effect assessment

5.2.6.1. Biological relevance considerations and historical control data for endpoint setting

Biological relevance

According to EFSA Scientific Committee (EFSA Scientific Committee, 2011; EFSA Scientific Committee, 2017a), a biologically relevant effect can be defined as 'an effect considered by expert judgement as important and meaningful for human, animal, plant or environmental health...'

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38

EFSA Journal 2023;21(2):7790

	OECD Nr.	Exposure	Reproductive parameters
	223	1 day	No
	205	5 days	No
ative	206	20 weeks	Yes

	OECD Nr.	Exposure	Reproductive parameters
	420, 423, 425	1 day	No
28-day toxicity study	407	28 d	No
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between short-term and long-term effects.

- There is no clear definition of short-term and long term in terms of duration
- Data on mammal toxicity is more extensive than for birds.

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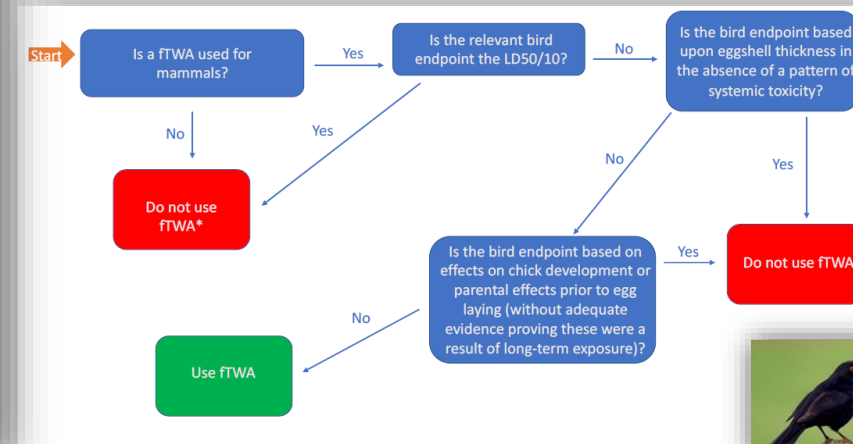
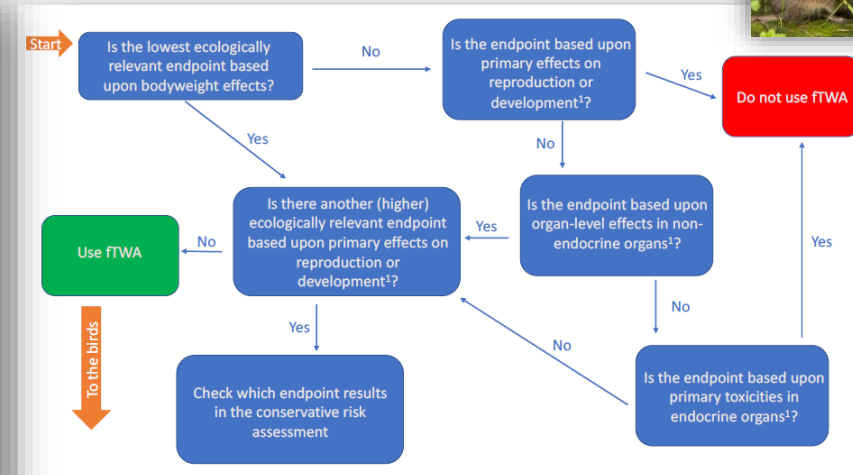
5 fTWA applicability check



Table 10: Examples of endpoints for which the fTWA is or is not appropriate*

	Mammals	Birds
Effects for which the fTWA is appropriate	Body weight and body weight change Food intake Liver and kidney effects Other organ-level effects (See Section 5.2.6.5)	Effects other than those specified in the following rows of this column
Effects for which case-by-case expert judgement should be employed	Effects on reproduction/development with some (parental) body weight or slight toxic effects Some tumours (see explanatory text above)	Effects on chick development which may be primary effects (i.e. unless a clear pattern of maternal toxicity is proven) Effects on parental birds as represented by body weight changes in females prior to egg laying (see explanatory text above)
Effects for which the fTWA should not be used	Primary reproductive effects (consult with mammalian toxicology and see Glossary and abbreviations); i.e. effects on fertility and fecundity not as a result of systemic toxicity Primary developmental effects (already judged sufficient for endpoint setting see Section 5.2.6.5); e.g. developmental effects in the absence of parental or systemic toxicity	Effects on eggshell thickness not correlated maternal bw/bw change/systemic toxicity When the LD ₅₀ /10 is lower than the endpoints from the avian reproduction study

*: The list is not exhaustive and is intended to provide guidance to the assessor and better guide harmonised decisions.



6 Primary vs secondary

Effects on reproduction and development

e.g., early resorption, post-implantation loss, late embryonic death, malformations, ...

Effects should not be considered as “primary” → Check for parental effects!

- Parental effects observed in female animals at lower or similar doses.
- Types of maternal toxicity observed in toxicological studies:
 - Mortality, significant weight loss, and clinical symptoms, ...
 - Reduced body weight gain and feed intake.
 - not considered for ecologically relevant endpoints.
 - Nevertheless, they may indicate general toxicity and effects on the females.
- More details on primary vs secondary effects are given in the second part (Ambiguities) of this workshop.

7a Examples

Study	Effect(s) driving the endpoint	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criteria 5	Conclusion
		Endpoint based on BW effects?	Endpoints based upon primary effects on repro/dev?	Endpoint based upon organ level effects in non-ED organs?	Endpoint based upon primary toxicities in ED organs?	Is there another (higher) relevant EP based upon primary effects on repro or dev?	Can the fTWA be used?
Mammal reproductive study	Bw ↓ > 10%	yes	no	no	no	no	yes
Mammal reproductive study	Bw ↓ > 10% Liver weight	yes	no	yes	no	no	yes
Mammal dev.tox . Study (rabbit)	early resorption post implant. loss Parental Bw ↓ < 10% (not population relevant) Organ weights, systemic tox (maternal bw ↓)	no	no Effects are secondary to maternal toxicity	yes	no	no	yes

7b Examples

Study	Effect(s) at endpoint	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Conclusion
		Is the fTWA used in mammals?	Is the endpoint based upon LD ₅₀ /10?	Is the endpoint based upon eggshell thinning in absence of systemic toxicity?	Is the endpoint based on chick development or parental effects prior to egg laying?	Can the fTWA be used?
Bird reproductive study	Bw change > 10%	yes	no	no	no	yes
Bird reproductive study	Eggshell thickness ↓ parental Bw gain ↓ > 10% systemic tox	yes	no	no Effects are secondary to maternal toxicity	no	yes

8a Examples

Study	Effect(s) at endpoint	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criteria 5	Conclusion
		Endpoint based on BW effects?	Endpoints based upon primary effects on repro/dev?	Endpoint based upon organ level effects in non-ED organs?	Endpoint based upon primary toxicities in ED organs?	Is there another (higher) relevant EP based upon primary effects on repro or dev?	Can the fTWA be used?
Mammal reproductive study	↑ pup mortality (>10%) post partum considered primary by Human health	no	yes	no	no	no	no
Mammal dev. tox . Study (rabbit)	Developmental malformations considered primary by Human health	no	yes	no	no	no	No

8b Examples

Study	Effect(s) at endpoint	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Conclusion
		Is the fTWA used in mammals?	Is the endpoint based upon LD ₅₀ /10?	Is the endpoint based upon eggshell thinning in absence of systemic toxicity?	Is the endpoint based on chick development or parental effects prior to egg laying?	Can the fTWA be used?
Bird reproductive study	Eggshell thickness ↓ cracked eggs ↑	yes	no	yes	yes	no
Bird reproductive study	Bw gain ↓ > 10% systemic tox	no*	no	no	no	no*
Bird reproductive study	Bw gain ↓ > 10% systemic tox	yes	yes*	no	no	no*

*An in-depth evaluation of data is needed on a case-by-case basis

➤ see presentations “Ambiguities” and “Non modelling lines of evidence”.

9 Unclear cases

- Mammals: Cases in which there are no clear conclusions in the human health section.
- Mammals: Cases where a re-evaluation of the findings of the toxicological studies is needed.
- Birds: When the LD₅₀/10 is from a limit dose study.
- Birds: What is the definition of the term “chick development”?

Even though the decision tree and table seem to provide guidance for the fTWA applicability assessment, there are still

- **a lot of questions,**
- **Uncertainties,**
- **Ambiguities related to the assessment,**

➤ that will be discussed in detail in the following presentations.



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Thank You

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