POSITION PAPER
25/04/2023 – POS/23/SN/36426

Water Treatment Guidance - CropLife Europe Proposal for an Assessment Scheme of water treatment transformation Products (tTPs)

Introduction

In September 2022, EFSA published a draft "Guidance Document on the impact of water treatment processes on residues of active substances or their metabolites in water abstracted for the production of drinking water" as a basis for a final guidance document to be published in 2023. The intention of this guidance document is to provide a tiered framework for the assessment of the impact of water treatment processes on residues of active substances (AS) of plant protection products (PPP) or biocidal products (BP) or its metabolites in surface water and/or groundwater abstracted for the production of drinking water, i.e., the formation of transformation products (TPs).

The draft Guidance Document (GD) contains a tiered hazard and risk assessment scheme to evaluate if water treatment TPs (tTPs) of BPs and PPPs pose a risk to human health (chapters 5 and 6 of the GD). During the commenting phase, it became evident that these two chapters would profit from some further input for the purpose of clarification, better structure and alignment with the principles agreed on OECD level for the toxicological assessment of dietary metabolites in the remit of revision of the OECD GD on the Definition of the residue (finalization by end of 2023 envisaged).

CLE commented intensively on the draft GD, mainly commenting, that:

- The current proposal is not sufficiently differentiating at lower tier (first exposure assessments use overly conservative dilution factors, lack of refinement options), and

- Has no efficient intermediate tier (data from existing studies, literature research, modelling, considering of pre- and post-treatment steps in water treatment).

Consequently, many substances may unnecessarily be subject to extensive higher-tier experimental testing and risk assessment. We like to emphasize that if chapter 2 and chapter 4 are not updated accordingly the obtained tTPs concentrations are an unreasonable "worst-case". There is a need for a more "realistic" exposure calculation before any animal toxicity tests are performed, and the tiered risk assessment will be conducted. For this purpose, CLE has drafted this position paper, focusing on chapter 5 "Hazard assessment" and chapter 6 "Tiered risk assessment" of tTPs:

- CLE welcomes the broad application of the Threshold of Toxicological Concern (TTC) concept as a pragmatic approach to assess a possibly large number of TPs.
- The central decision tree for the tiered risk assessment (Figure 8) is a good starting point but has several shortcomings and errors and contains several contradictions with the text of the draft GD; see detailed comments submitted in October 2022.
- In the following, CLE will present a proposal of an assessment scheme for hazard (Tier 1-2) and tiered risk assessment (Tier 3A-B and Tier 4).
- Please note that the nomenclature of the tiers and stages in the CLE proposal is different than in the draft GD for a better differentiation of refinement options.
- The draft GD contains a very unspecific Tier 3 risk assessment ("based on endpoints other than genotoxicity and repeated dose toxicity") which is not included in the following CLE proposal as it is unclear from the given explanations, which endpoints need to be further addressed and it is also seen as introducing new risk assessment requirements currently not in force for PPP and BP.

Executive Summary of Proposal

The **hazard assessment** is performed for individual tTPs, which occur in amounts > 0.075 µg/L[I] as proposed in chapter 4.2.7 of the draft GD, unless the TTC concept is found to be not applicable. Because tTPs concentrations obtained with the procedures from the draft GD from September 2022 are overly conservative and highly unrealistic, realistic exposure values should be used. Realistic exposure values can for example be derived from landscape level occurrence data considering the specific crops and use areas of the AS or consider the impact of treatment combinations (as standardly applied in waterworks) on the levels of precursors and tTPs. All individual tTPs > 0.075 µg/L will be **evaluated for their genotoxic properties (Tier 1);** in the absence of compound-specific genotoxicity data, this assessment is based on (Q)SAR/Read-across. In case of a concern, genotoxicity testing of tTP or a group lead compound (Ames and/or *in vitro* MNT followed by targeted *in vivo* testing, in case of positive results)[II] should be carried out. In case of inconclusive, contradictory, or equivocal results, it may be appropriate to conduct further testing *in vitro* (EFSA 2011). If - based on the data - the tTP is concluded to be genotoxic, human dietary exposure needs to be limited to not exceed 0.0025 µg/kg bw/d (for any population group) with appropriate risk mitigation measures.

All tTPs shown to be without genotoxicity concern will proceed to a **general toxicity assessment (Tier 2)**. If data are already available for the respective tTP or a similar[III] substance which can be used for read-across and if these data are adequate and sufficient to derive a HBGV, it can be proceeded to the Tier 3 risk assessment. If no data are available, the TTC concept can be used to avoid unnecessary animal testing and to decide if targeted toxicity testing is necessary. Exposures of the tTP should be checked against the respective applicable TTC thresholds (TTC for organophosphates/carbamates or Cramer Class III, corresponding to 9 µg/L or 45 µg/L if water is the only exposure route) and if they are below these thresholds, assessment can be concluded with no health concern. If “realistic” exposure exceeds these thresholds, targeted toxicity testing should be conducted with the aim to derive suitable HBGVs and allowable drinking water concentrations.

The last step is the actual **risk assessment (Tier 3 and 4)**, which is proposed as a tiered approach. The 1st Tier (Tier 3A) of the proposed risk assessment is based on available exposure data of the respective active substance, using realistic concentrations of the tTP. A risk assessment with refined (drinking water) exposure data should follow, if necessary, as a 2nd Tier (Tier 3B). The Higher Tier risk assessment (Tier 4), considering all sources of dietary exposure, should be accomplished by the risk managers/assessors retrospectively using refined exposure data (e.g. from monitoring) and possible probabilistic tools. The requirement in the draft GD to aggregate exposure from different sources will be challenging if the additional sources are different AS or unrelated to PPPs and agriculture (e.g. common treatment products from industrial chemicals, pharmaceuticals, or natural compounds), as the necessary exposure data will not be available to the applicant. Therefore, the two cases should be differentiated:

- Aggregate exposure considering all sources within the same active substance/biocidal products (e.g. if the treatment product is identical to a plant/livestock metabolite) (**Tier 3A and B**)
- Aggregate exposure considering additional sources related to different active substances/biocidal products or sources not related to agriculture (e.g. common treatment products from industrial chemicals, pharmaceuticals, or natural compounds) (**Tier 4**).

In all steps involving exposure, this is understood as exposure of either the individual tTP or – if relevant- the summed exposure of similar tTPs (grouped according to the ECHA and OECD principles and sufficiently supported by a scientifically sound similarity assessment).

[I] Corresponds to the threshold of 0.15 µg/person/day set by the EFSA for the ‘Threshold of Toxicological Concern’ with regards to potential DNA-reactive mutagens and/or carcinogens (EFSA 2019) taking into account a consumption of 2 L water per day

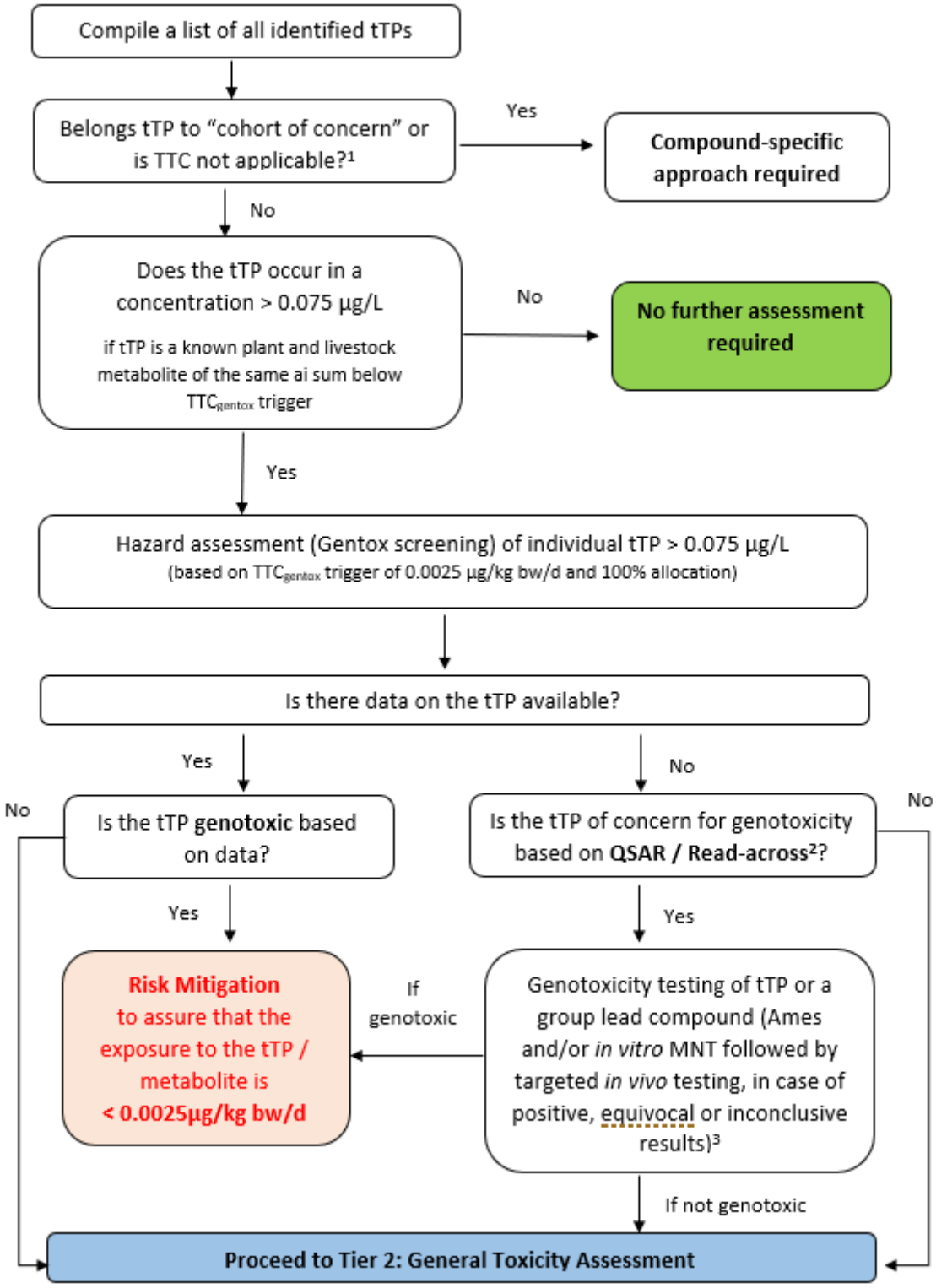
[II] Future OECD Guidance on Residue Definition (expected 2023), OECD Guidance on grouping and read across (OECD, 2014),

[III] Similarity assessment by comparison of e.g. structural similarity, Phys/Chem properties, toxicophore analysis, mechanistic and ADME data, …), to be aligned with the future OECD GD on Residue Definition (expected 2023)

Proposed Assessment Scheme

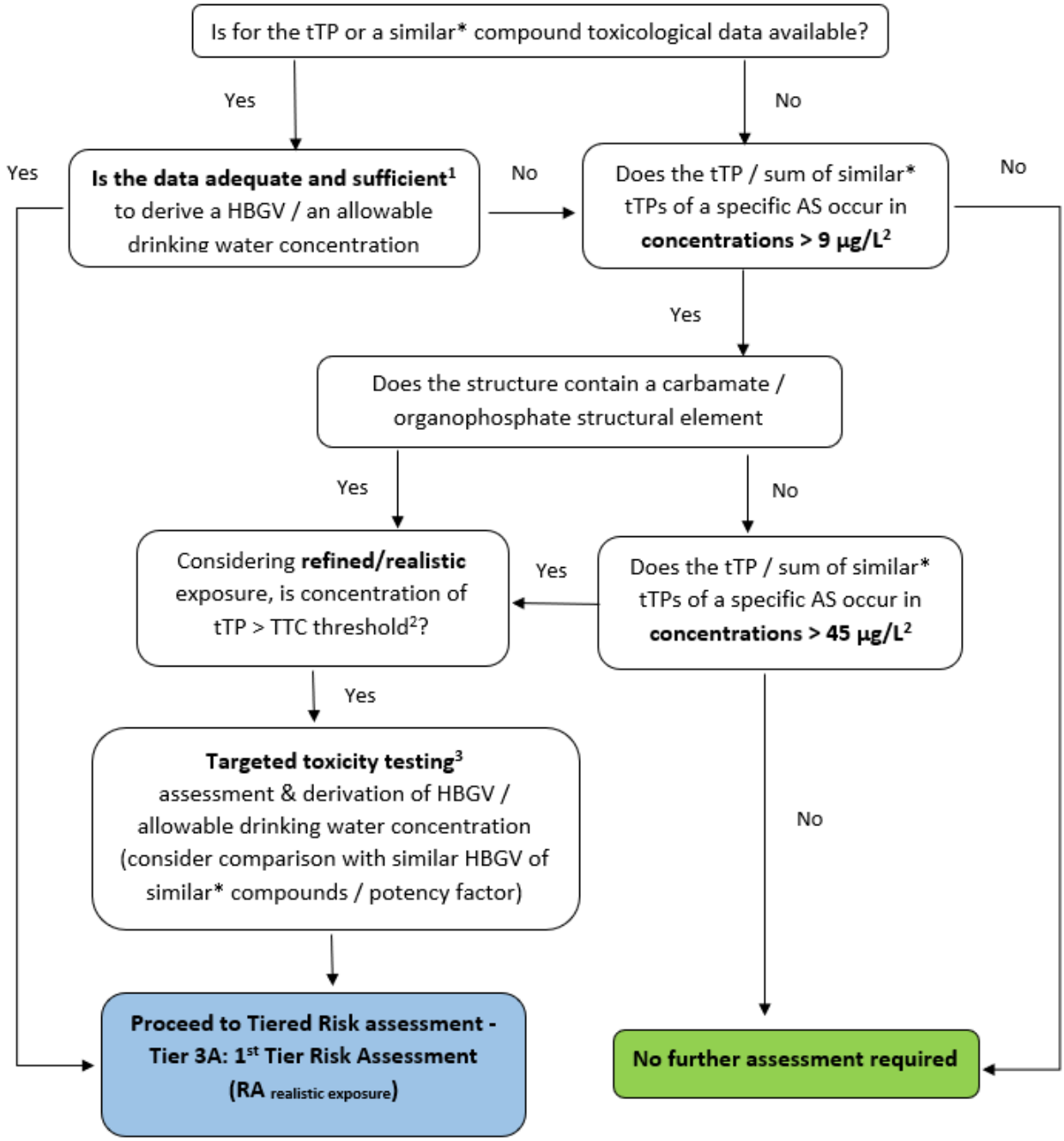
Tier 1 – Genotoxicity Assessment

[1] EFSA (2019a), EFSA Journal 2019, 17(6), 5708, DOI: 10.2903/j.efsa.2019.5708; as for plant and livestock metabolites in OECD GD on RD for Read-across 2023



[2] EFSA (2019b), EFSA Supporting publication2019:EN-1598; DOI 10.2903/sp.efsa.2019.EN-1598
[3] EFSA (2011); EFSA Journal 2011;9(9):2379), DOI 10.2903/j.efsa.201122379

Tier 2 – General Toxicity Assessment



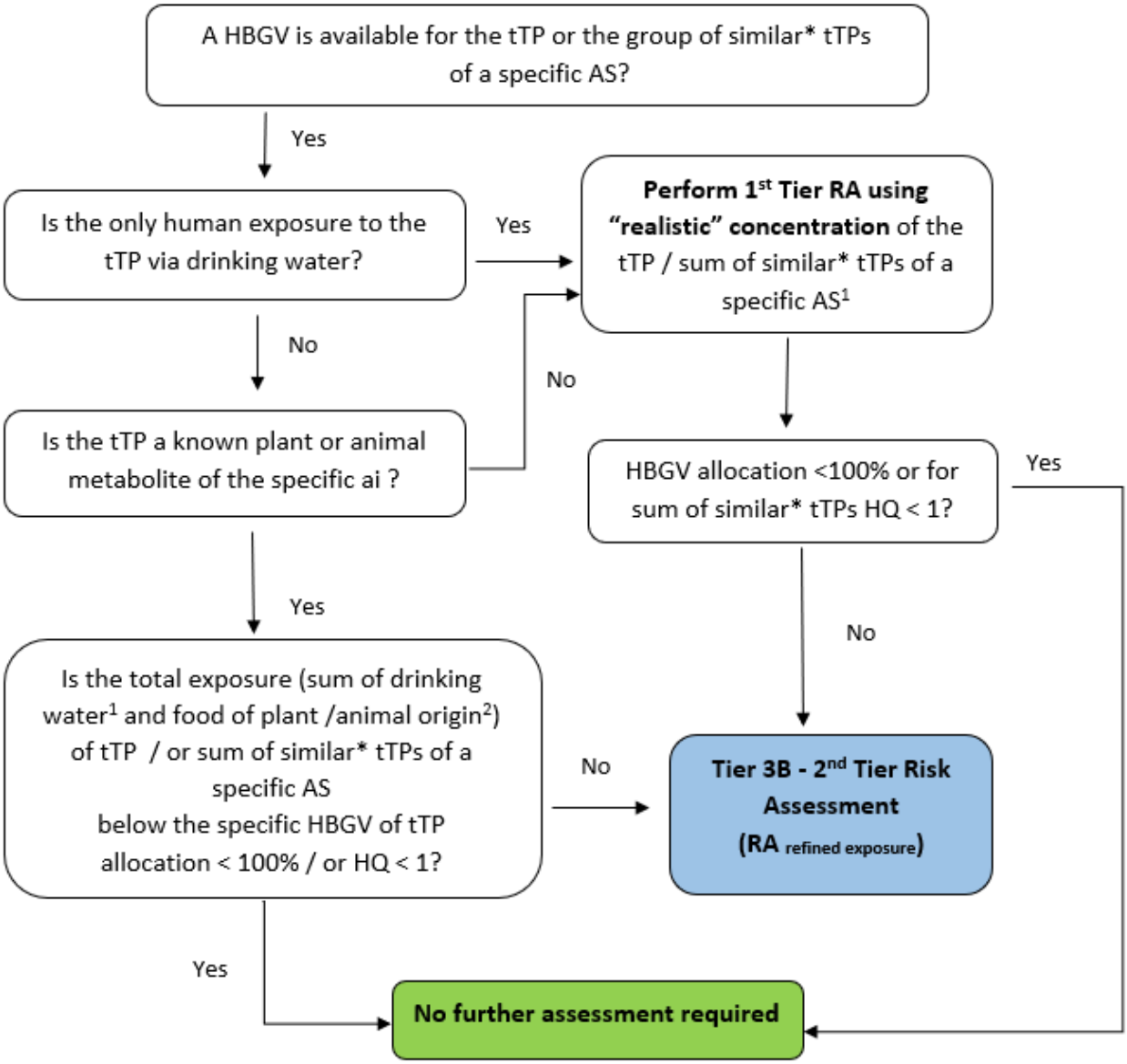
* Similarity assessment by comparison of e.g. structural similarity, physical/chemical properties, toxicophore analysis, mechanistic and ADME data, …

[1] Considering data / toxicological properties of similar* compounds

[2] if tTP is a known plant and livestock metabolite of the same AS sum below TTC for OPs/carbamates of 0.3 µg/kg bw/d or TTC for Cramer Class III 1.5 µg/kg bw/d;

[3] aligned with the future OECD GD on the definition of residue / including expert judgement

Tier 3A – 1st Tier Risk Assessment (RA realistic exposure)

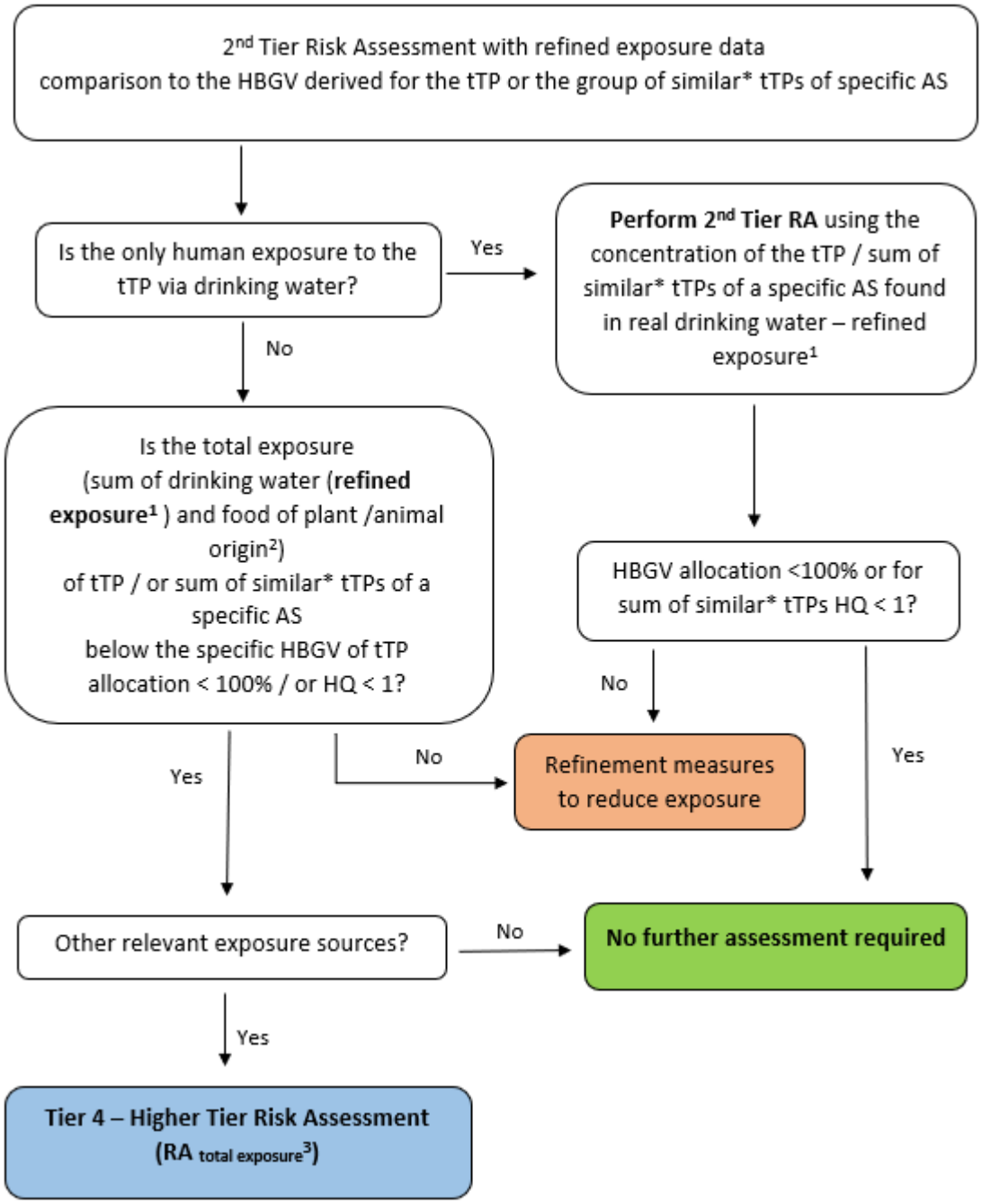


* Similarity assessment by comparison of e.g. structural similarity, physical/chemical properties, toxicophore analysis, mechanistic and ADME data, …

[1] WHO consumption data and body weights (2 L 60 kg, 1 L 10 kg, 0.75 L 5 kg) or in EFSA Primo revision 4

[2] EFSA 2023 - EFSA PRIMo v4, Pesticide Residue Intake Model – PRIMo revision 4

Tier 3B – 2nd Tier Risk Assessment (RA refined exposure)



* Similarity assessment by comparison of e.g. structural similarity, physical/chemical properties, toxicophore analysis, mechanistic and ADME data, …

[1] WHO consumption data and body weights (2 L 60 kg, 1 L10 kg. 0.75 L 5 kg) or in EFSA Primo revision 4

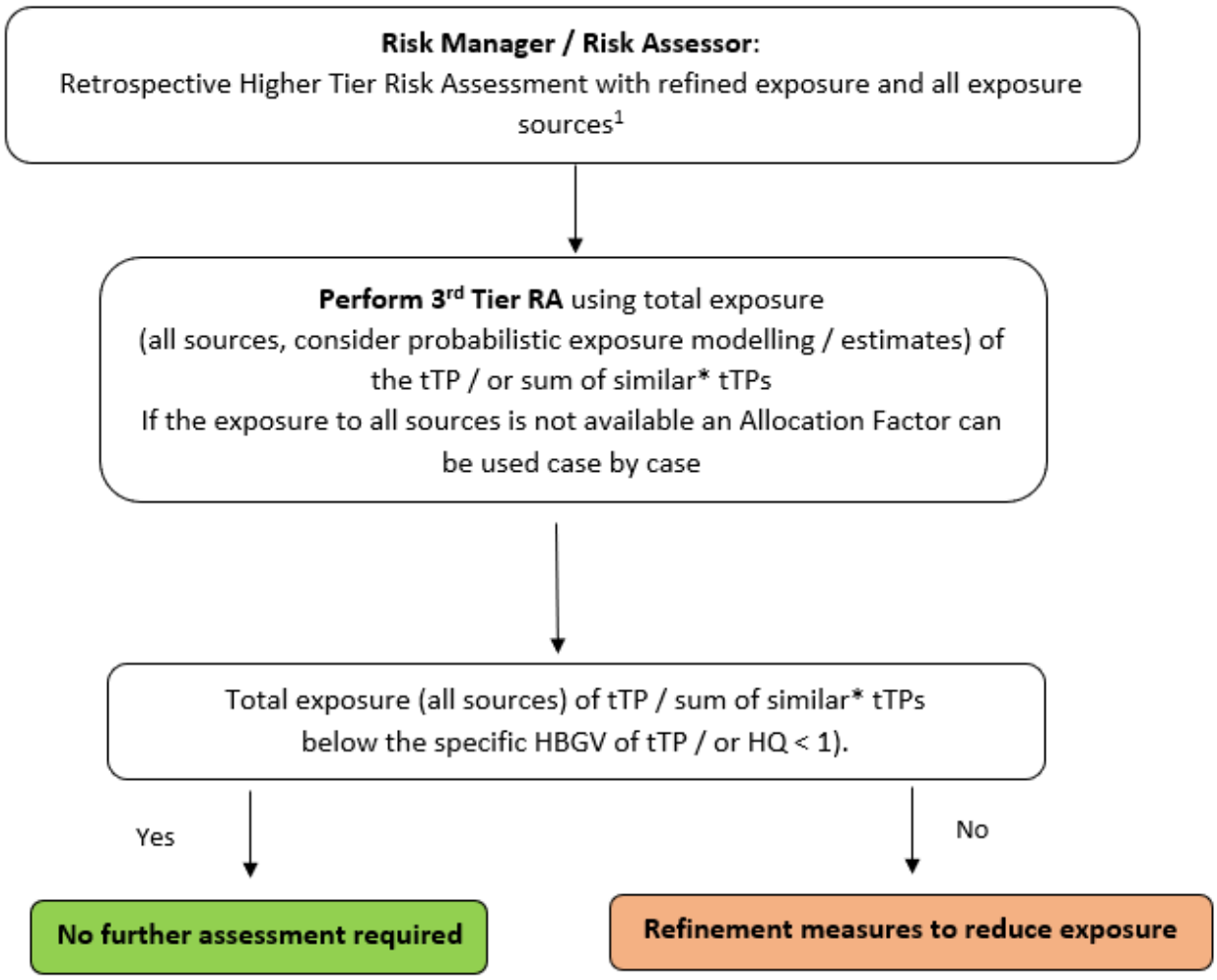
[2] EFSA 2023 - EFSA PRIMo v4, Pesticide Residue Intake Model – PRIMo revision 4

[3] Total exposure in the retrospective Tier 4 RA considers exposure from all known sources (e.g. common tTP or metabolite to different AS, or is not related to agriculture e.g., common treatment products from industrial chemicals, pharmaceuticals, or natural compounds)

Tier 4 – Retrospective Higher Tier Risk Assessment (RA $_{\text{total exposure}}$)

It should be noted that TPs can be formed from many precursors.
The most prevalent source of TPs precursors entering drinking water treatment plants is natural organic matter. The amount and composition of natural substances entering a drinking water treatment plant depend on local conditions and vary seasonally. Anthropogenic contaminants only contribute to a small extend and typically only occur seasonally.

As identical TPs can be formed from natural and anthropogenic substances, the applicant is not in capacity to conduct a higher Tier (Tier 4) exposure assessment with the respective allocation of an HQ. Development of probabilistic exposure models to retrospectively estimate human exposures is encouraged.



* Similarity assessment by comparison of e.g. structural similarity, physical/chemical properties, toxicophore analysis, mechanistic and ADME data,

[1] Total exposure from all known sources (e.g. common tTP or metabolite to different AS, or is not related to agriculture, e.g., common treatment products from industrial chemicals, pharmaceuticals, or natural compounds)…

Explanatory Notes

Tier 1: Genotoxicity Assessment

The Genotoxicity assessment starts with the compilation of a list of all identified tTPs (according to chapter 4 of the draft GD). If a tTP belongs to a "Cohort of concern (CoC)"[IV] (Kroes et al, 2004) or the TTC concept (EFSA 2019) is not applicable, a compound specific approach is needed for the assessment. If the TTC concept can be used it should be checked whether the tTP occurs in a concentration above 0.075 µg/L[I]. It should be considered that tTPs concentrations obtained with the procedures from the draft GD dated September 2022 are overly conservative and highly unrealistic. Before proceeding to the risk assessment, potentially triggering animal testing, realistic exposure calculations should be conducted. Realistic exposure calculations should for example include landscape level exposure calculations considering the specific crops and use areas of the AS or consider the impact of treatment combinations (as standardly applied in waterworks) on the levels of precursors and tTPs**.** In case the tTP is also a known plant and / or livestock metabolite of the same AS, the combined exposure of tTP/metabolite should be compared to the TTC for DNA-reactive substances, i.e. 0.0025 µg/kg bw/d. In case the combined exposure of tTP / metabolite is below 0.0025 µg/kg bw/d no further assessment is required (EFSA 2019a).

In case the exposure of the individual tTP is above 0.075 µg/L, a hazard assessment (genotoxicity screening) is required. The genotoxicity screening starts with a check if there are experimental genotoxicity data available. In case there are data available that indicate that the tTP is genotoxic, risk mitigation measures and/or refined exposure assessment need to be applied to assure that the refined exposure[V] of the tTP / metabolite is below 0.0025 µg/kg bw/d. Refined exposure assessment can for example include monitoring data to evaluate the actual level of occurrence of the precursor(s) in raw waters at abstraction location or the tTP in treated waters or monitoring of the TPs in actual drinking water. In case experimental data show that there is no concern for genotoxicity the tTP should be proceeded to Tier 2 – General Toxicity Assessment.

If there is no experimental data for the tTP available, the genotoxicity potential should be assessed by (Q)SAR and read-across. The (Q)SAR and read-across assessment should be in-line with other guidance documents[II]. If the (Q)SAR / read-across assessment can reliably exclude a concern for genotoxicity, the tTP should proceed to Tier 2. In case the (Q)SAR / read-across assessment provides a concern of equivocal outcome or is inconclusive, genotoxicity testing should be considered. Based on the results of the (Q)SAR / read across assessment an Ames test and/ or *in vitro* MNT should be conducted (EFSA 2011). If a grouping of tTPs/metabolites can be established, testing of a lead compound of that group is sufficient. In case of positive results, targeted *in vivo* genotoxicity testing is required. In case of inconclusive, contradictory, or equivocal results, it may be appropriate to conduct further testing *in vitro* before *in vivo* testing is initiated (EFSA 2011). If the outcome of the genotoxicity testing shows that the tTP has a genotoxic potential, risk mitigation measures and/or refined exposure assessment (see above) need to be implemented. In case the genotoxicity tests show that there is no concern for genotoxicity, the assessment should proceed to Tier 2: General Toxicity Assessment taking into account realistic exposure.

Tier 2: General Toxicity Assessment

The General Toxicity Assessment starts with a check if there are toxicological data for the tTP or a similar[III] compound available. If data are available and adequate and sufficient to derive a Health-Based Guidance Value (HBGV) and / or allowable drinking water concentration, the assessment should proceed to the Tier 3: Tiered Risk Assessment. In case there is no data or no adequate/sufficient data on the tTP or similar[III] compound available, it is checked if the concentration of the tTP or sum of similar tTPs (if grouping approach applies) of the same AS is below 9 µg/L. In case the tTP is also a plant and / or livestock metabolite it needs

[IV] aflatoxin-like compounds, N-nitroso-compounds, azoxy-compounds, steroids, and polyhalogenated dibenzo-p-dioxins and-dibenzofurans.
[V] Refined exposure = realistic exposure.

to be checked if the combined exposure is below 0.3 µg/kg bw/d. If this is the case no further assessment is required for the tTP (group of tTPs).

In case the individual concentration of the tTP is above 9 µg/L or combined exposure is above 0.3 µg/kg bw/d, it needs to be checked if the tTP contain a neurotoxic carbamate or organophosphate (OP) structural element.

In case the tTP does not contain an organophosphate (OP) or neurotoxic carbamate structural element and the sum of similar tTPs is below 45 µg/L (combined below 1.5 µg/kg bw/d), no further assessment is required.

If the tTP contains an organophosphate or neurotoxic carbamate structural element or if the concentration is above 45 µg/L, or the combined exposure of tTP and plant / livestock metabolites of the same AS is above 1.5 µg/kg bw/d, a refined / realistic exposure of the tTP should be compared to the respective TTC threshold.

Please note that tTPs concentrations obtained with the procedures from the draft GD dated September 2022 are overly conservative and highly unrealistic. Before proceeding to the risk assessment, potentially triggering animal testing, realistic exposure calculations, using WHO consumption data for adults (2 L/day) and bodyweights (60 kg),should be conducted. Realistic tTP concentrations should for example include landscape level exposure calculations considering the specific crops and use areas of the AS or consider the impact of treatment combinations (as standardly applied in waterworks) on the levels of precursors and tTPs.

If the refined / realistic exposure is above the respective TTC threshold targeted toxicity testing is required to derive a HBGV / allowable drinking water concentration for the Tier 3: Tiered Risk Assessment.

Tier 3: Tiered Risk Assessment

Tier 3A - Risk Assessment – realistic exposure

The Tier 3A of the Risk Assessment uses the derived HBGV for the tTP or group of similar tTPs of a specific AS and realistic exposures. If the exposure to the tTP is only via drinking water, realistic exposures calculated with realistic concentration of the tTP and the WHO consumption data and bodyweights (2 L 60 kg, 1 L10 kg, 0.75 L 5 kg) or in future using the drinking water consumption data from EFSA Primo 4. If the exposure is below 100% allocation of the HBGV or the Hazard Quotient (HQ) for the combined exposure of similar tTPs of the same AS is below 1, no further assessment is required. In case the HBGV is exceeded, or the HQ is above 1, the 2nd Tier risk assessment using refined exposure data needs to be done (Tier 3B).

If the exposure to the tTP is not only via drinking water but also via plant and/or livestock metabolites of the same AS, the total exposure needs to be below the HBGV of the tTP or HQ needs to be below 1, otherwise 2nd Tier risk assessment using refined exposure data needs to be done (Tier 3B). The total exposure should always be calculated separately, and the total calculated for the same population group (e.g. NL toddler), to see the driver of the exposure and decide on possible mitigation measures.

Tier 3B – Risk Assessment – refined exposure

The Tier 3B of the Risk Assessment uses the derived HBGV for the tTP or group of similar tTPs of a specific AS and refined exposure values. If the exposure to the tTP is only via drinking water, a 2nd Tier Risk Assessment will be performed using refined concentrations of the tTP or sum of similar tTPs, calculated with refined concentration of the tTP. The refined tTP concentrations will then be combined with the WHO consumption data and bodyweights (2 L 60 kg, 1 L10 kg, 0.75 L 5 kg) or for future registration purposes, a suitable EFSA Primo 4 when available. The refined exposure assessment aims at evaluating the actual level of occurrence of the tTP in real treated waters and can for example include monitoring data for the precursor in raw waters at abstraction location or for the TP in treated drinking water. If the exposure is below 100% allocation of the HBGV or the Hazard Quotient (HQ) for the combined exposure of similar tTPs is below 1, no further assessment is required. In case the HBGV is exceeded, or the HQ is above 1, refinement measures to reduce the exposure are needed (e.g. less critical GAP).

If the exposure to the tTP is not only via drinking water but also via plant and/or livestock metabolites of the same AS, the total exposure needs to be below the HBGV of the tTP or HQ needs to be below 1 or refinement

measures to reduce the exposure are needed (e.g. less critical GAP). The total exposure should always be calculated separately, and the total calculated for the same population group (e.g. NL toddler), to see the driver of the exposure and decide on possible mitigation measures.

Tier 4: Retrospective Higher Tier Risk Assessment

Higher Tier Risk Assessment – total exposure (i.e. all exposure sources)

It should be noted that TPs can be formed from many precursors.
The most prevalent source of TPs precursors entering drinking water treatment plants is natural organic matter. The amount and composition of natural substances entering a drinking water treatment plant depend on local conditions and vary seasonally. Anthropogenic contaminants only contribute to a small extend and typically only occur seasonally.

Identical TPs can be formed from multiple biotic and abiotic sources. For example depending on the experimental conditions of ozonation benzoic acid can be formed from humic acid, diverse phytotoxins and biotic compounds. In combination with chlorination benzoic acid will then lead to the formation of small molecular chlorinated alkyl derivatives.

Another example is the formation of halogenated benzoquinones originating from diverse phenolic substructures liberated by UV treatment or ozonation (see Zhao et al (2012). Such a situation is certainly given for multiple structural elements (e.g. phytogenic esters and cleavage of glucosides).

A list of small molecular halogenated TPs has previously been defined in Hebert (2010). It is scientifically not possible to differentiate the exposure source of such small molecular TPs.

Therefore, the applicant will not be able to do a higher Tier (retrospective Tier 4) exposure assessment with the respective allocation of an HQ.

If other relevant exposure sources are known a higher tier RA (Tier 4) considering all exposure sources can be considered post-registration of a specific AS. This retrospective higher Tier Risk Assessment with refined exposure data and all exposure sources (e.g., common tTP or metabolite to different AS, or is not related to agriculture e.g., common treatment products from industrial chemicals, pharmaceuticals, or natural compounds), to the HBGV derived for the tTP or the group of similar tTPs should be steered by the risk managers/ risk assessors, as the necessary exposure data will not be available to the applicants. Probabilistic exposure modelling and estimates should be used, If the exposure to all sources is not available an Allocation Factor can be used case by case (see also draft GD Appendix 7). Total exposure (all sources) of tTP or sum of similar[III] tTPs should below the specific HBGV of tTP or HQ needs to be below 1, then no further assessment is required, otherwise refinement measures to reduce the exposure are needed (e.g. less critical GAP, pre- and post- treatment steps in water works etc.).

References

EFSA 2011 - Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment; EFSA Journal 2011;9(9):2379; DOI 10.2903/j.efsa.2011.2379

EFSA, 2019a – Guidance of the use of Threshold of Toxicological Concern approach in food safety assessment; EFSA Journal 2019; 17(6):5708; DOI: 10.2903/j.efsa.2019.5708

EFSA, 2019b - Evaluation of the applicability of existing (Q)SAR models for predicting the genotoxicity of pesticides and similarity analysis related with genotoxicity of pesticides for facilitating of grouping and read across, EFSA Journal

Hebert et al. (2010) - Innovative method for prioritizing emerging disinfection by-products (DBPs) in drinking water on the basis of their potential impact on public health; Water Research 44; 3147-3165

Kroes et al. 2004 - Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet; Food and Chemical Toxicology 42 (2004) 65–83

OECD 2014 - Series on Testing and Assessment No. 194: Guidance on Grouping of Chemicals, Second Edition. ENV/JM/MONO(2014)4, available at http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publicationsnumber.htm

OECD (2023) - OECD Guidance on the definition of residues (expected 2023),

Zhao et al (2012) - Occurrence and formation of chloro- and bromo-benzoquinones during drinking water disinfection; Water Research 46 (2012) 4351-4360.

Annex I – Abbreviations / Definitions

AS	Active substance
BP	Biocidal Product
CLE	Crop Life Europe
CoC	Cohort of concern
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
GAP	Good Agricultural Practice
GD	Guidance Document
HBGV	Health Based Guidance Value
HQ	Hazard Quotient
MNT	Micronucleus Test
OECD	Organization for Economic Co-operation and Development
OP	Organophosphate
PPP	Plant protection product (i.e. pesticide)
(Q)SAR	(Quantitative) Structure-Activity Relationships
RA	Risk Assessment
TP	Transformation product
TTC	Threshold of Toxicological Concern
tTP	(water) Treatment transformation product
WHO	World health Organization