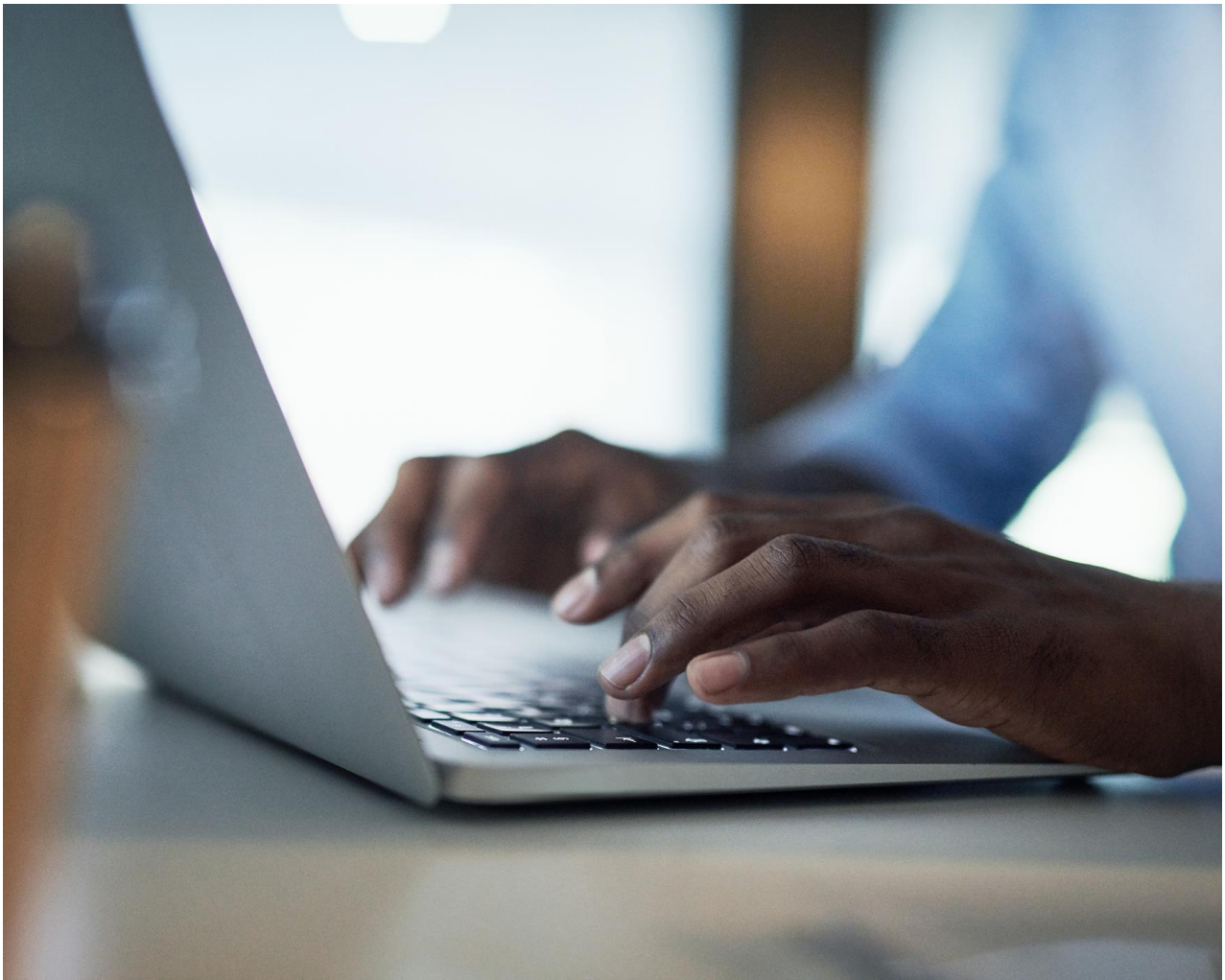
TTC and groundwater metabolites

Use of the Threshold of Toxicological Concern (TTC) Cramer Class III (CCIII) value at step 5 of the groundwater (gw) metabolite relevance assessment of PPPs

February 2022



Contents

Issue

1. HSE favours the use of the TTC CCIII value (1.5 µg/kg bw/d) for groundwater (gw) metabolites at step 5 (refined risk assessment) of the relevance assessment of PPPs, when there are no other suitable data to derive metabolite-specific acceptable daily intakes (ADIs). HSE considers it to be a scientifically valid approach which is consistent with the SANCO (2003)[1] gw relevance assessment guidance (the EU guidance currently applicable in Great Britain-GB and Northern Ireland-NI, relevant to this specific aspect of the evaluation).

2. The TTC approach is a pragmatic, scientifically valid methodology to assess the oral safety of substances when hazard data are incomplete (EFSA, 2019)[2]

3. Detailed examination of the approach described in the SANCO (2003) guidance has raised a number of questions regarding the scientific merits of the TTC CCIII value and its applicability to step 5 of the relevance assessment. Reference material relevant to this paper is provided in Annex A.

4. The SANCO guidance has not been updated since 2003 to take account of technical and scientific progress in its decision-making; the TTC approach in its current form (EFSA, 2019) has become a widely accepted regulatory tool.

5. The TTC CCIII value is very conservative, more conservative than any ADI HSE could set using specific animal data on the metabolites; hence it maintains high standards of protection in GB. After excluding genotoxicity, the TTC CCIII value represents the reference value for one of the most toxic chemicals (excluding organophosphates and carbamates) from a large database of substances with adequate data. In the SANCO guidance scheme, genotoxicity needs to be excluded (based on actual negative experimental data, rather than lack of structural alerts) at step 3, in order to proceed to the next step. Therefore, use of the TTC CCIII value in step 5 is clearly supported by robust negative experimental data.

6. HSE is committed to minimise unnecessary animal testing, with *in vivo* vertebrate studies being seen as the last resort (Art. 62 of Regulation (EC) No 1107/2009). For metabolites which are not structurally or toxicologically similar to the parent active substance or for which a read-across from a data-rich analogue is not possible, the SANCO (2003) guidance requires at step 5 the generation of repeated dose toxicity studies in experimental animals to establish metabolite-specific ADIs for the subsequent dietary risk assessment. This paper describes when the TTC CCIII value

[1] SANCO (2003) guidance; Assessment of the relevance of metabolites in groundwater, directive 91/414EEC (europa.eu)

[2] EFSA (2019) TTC guidance; Guidance on the use of the Threshold of Toxicological Concern (europa.eu)

can be used as an alternative to studies in experimental animals, leading to a significant reduction in unnecessary animal testing. However, it should only be used when it is considered scientifically justified, in line with the most recent EFSA guidance (2019) on TTC.

7. The TTC approach has already been used for dietary (plant and livestock) metabolites by HSE in some applications for extension of authorisation for minor use (EAMU) and in the EU for some active substance assessments.

8. The TTC CCIII, being such a low value, might not lead to an acceptable risk; hence it is not a guarantee for authorisation. The TTC CCIII is part of a tiered approach which can be refined further if necessary.

Annex A

Reference material

SANCO (2003) guidance; Assessment of the relevance of metabolites in groundwater, directive 91/414EEC (europa.eu)

Relevant extract from the SANCO guidance

Step 4: Exposure assessment - threshold of concern approach

Metabolites which have not been identified as being relevant according to the hazard screening outlined in Step 3, should be further tested in an exposure assessment to make sure that any contamination of groundwater will not lead to unacceptable exposure of consumers via their drinking water. Such an assessment, if done in isolation, would require, in principle, a full set of toxicological data according to Annex II of the Directive to ultimately establish an Acceptable Daily Intake value for these substances and is not excluded in Step 5 below. However, as a pragmatic alternative in cases where a full quantitative risk assessment cannot be provided, an approach following a "threshold of concern" should be followed. The approach is based on a statistical evaluation of lifetime carcinogenicity studies for more than 500 substances, which were originally compiled by Gold et al. 1989[3] and later supplemented and refined by other authors. Both, the Scientific Committee on Plants[4] and the Scientific Committee on Food[5] have discussed this concept and found that the available scientific information base is sufficiently large to consider an application of a threshold of toxicological concern as a concept, which is rational, pragmatic and scientifically valid. Following this concept, for substances of unknown structure the Scientific Committee on Plants proposed a toxicological threshold of concern of 1.5 µg/person/day or 0.02 µg/kg body weight/day[6], which is in line with the threshold developed by the US-FDA.

3 Gold et al. 1989
4 SCP 2000
5 SCF, 1996
6 Munro et al., 1996; Munro et al., 1999.

Assuming a consumption of 2 liters of water per day[7], all of which comes from the upper soil layer, such an acceptable exposure level relates to an acceptable estimated upper limit for the concentration of a metabolite of 0.75 µg/L. When carrying out this assessment, it must be checked whether there is potential exposure for consumers via other sources but drinking water, e.g. if the metabolite in question is also found among the residues on treated commodities. Such a potential exposure from other sources should be taken into account in order to ensure that total exposure of consumers to the metabolite will not exceed the acceptable overall threshold of concern of 0.02 µg/kg body weight/day. Such a threshold can only be considered acceptable if the metabolite in question - does not exceed 0.75 µg/L (or a lower level, if consumers are exposed also via other routes) and has passed Step 3 i.e.

- has a lower biological activity than the parent,

- is not genotoxic and

- is not defined as toxic.

Substances for which all metabolites meet all these criteria can be further considered for Annex I inclusion. Where there is insufficient information to do a satisfactory assessment at this Step, then a refinement is necessary and further data will be required in Step 5.

Step 5: Refined risk assessments for non-relevant metabolites

Metabolites which have passed steps 1 to 3 and for which levels of estimated concentrations of metabolites in groundwater (as defined in Step 2) lie between 0.75 µg/L (from Step 4) and 10 µg/L will require a refined assessment of their potential toxicological significance for consumers. All such metabolites, which are estimated to occur at levels exceeding the toxicological threshold for unknown substances, must be fully identified and also synthesised by the notifier, if necessary to allow their further testing.

The appropriate strategy for the assessment of these cases has to be developed on a case-by-case basis in collaboration between the notifier and the Rapporteur Member State.

[7] Which is a conservative value also recommended by WHO (1994).

As a general principle, it should be understood that data requirements raised in this context do not always have to be addressed by experimental studies. Notifiers may, if possible, address open questions by using available information in support of a scientific and rational assessment. Valuable sources of information include, but are not limited to:

- consideration of molecular structure of the metabolite (active part intact?);
- the occurrence of metabolites in existing tests with the active substance;
- general knowledge on the relationship between the toxicity of metabolites and their parent substances;
- available knowledge on related compounds.

In such cases expert judgement may be used to determine the necessity of requiring additional information. With regard to human toxicology it should be investigated in particular whether a metabolite was also identified in mammalian laboratory animals and, consequently, has been intrinsically subject to toxicity studies along with the active substance. The occurrence of metabolites, their quantification and the extrapolation of this information to humans should be based on expert judgement, taking into consideration known differences in phase one and two metabolism and assessments of biochemical plausibility. For example, a metabolite formed in soil, which may be present in groundwater may be a plausible metabolite in mammals, which is only transient and, therefore, not detectable in significant quantity in laboratory animals. Conjugates formed in biotic processes in the soil may be readily cleaved in the gastro-intestinal tract and may give rise to known metabolites in mammals. If the metabolite is found in laboratory animals, the acceptable limit in groundwater for this compound may be defined on the basis of existing studies with the active substance.

If a metabolite is not likely to be formed in laboratory animals upon exposure to the active substance, stepwise testing should be conducted to determine the full toxicological profile of the metabolite or to generate enough information to allow a comparison with the toxicology profile of the active substance to be made. The extent of the toxicology testing should be determined by expert judgement on a case-by-case basis, but the investigation of potential genotoxicity will probably represent the first step in most cases. The notifier should always be required to provide justification when a full toxicological profile is not produced. Possible reasons for avoiding unnecessary testing include the use of existing information on alerting structures (SAR), or toxicological information derived from structurally related chemicals.

EFSA (2019) TTC guidance; Guidance on the use of the Threshold of Toxicological Concern (europa.eu)

Relevant extract from the EFSA TTC guidance:

The Scientific Committee confirms that the Threshold of Toxicological Concern (TTC) is a pragmatic screening and prioritisation tool for use in food safety assessment. This Guidance provides clear step-by step instructions for use of the TTC approach. The inclusion and exclusion criteria are defined and the use of the TTC decision tree is explained. The approach can be used when the chemical structure of the substance is known, there are limited chemical-specific toxicity data and the exposure can be estimated. The TTC approach should not be used for substances for which EU food/feed legislation requires the submission of toxicity data or when sufficient data are available for a risk assessment or if the substance under consideration falls into one of the exclusion categories. For substances that have the potential to be DNA-reactive mutagens and/or carcinogens based on the weight of evidence, the relevant TTC value is 0.0025 µg/kg body weight (bw) per day. For organophosphates or carbamates, the relevant TTC value is 0.3 µg/kg bw per day. All other substances are grouped according to the Cramer classification. The TTC values for Cramer Classes I, II and III are 30 µg/kg bw per day, 9 µg/kg bw per day and 1.5 µg/kg bw per day, respectively. For substances with exposures below the TTC values, the probability that they would cause adverse health effects is low. If the estimated exposure to a substance is higher than the relevant TTC value, a non-TTC approach is required to reach a conclusion on potential adverse health effects.

TTC values – classification of substances

Classification	TTC value in µg/person/d	TTC value in µg/kg bw/d

Potential DNA-reactive mutagens and/or carcinogens	0.15	0.0025
Organophosphates and carbamates	18	0.3
Cramer Class III	90	1.5
Cramer Class II	540	9
Cramer Class I	1800	30

Further information

For information about health and safety, or to report inconsistencies or inaccuracies in this guidance, visit the HSE website (www.hse.gov.uk).

You can order HSE priced publications at the HSE Books website (https://books.hse.gov.uk).

HSE priced publications are also available from bookshops.

This publication is available at https://www.hse.gov.uk/pesticides/resources/T/tcc-and-groundwater-metabolites.pdf

Published by the Health and Safety Executive 02/22.