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# Toxicological risk assessment and prioritization of drinking water relevant contaminants of emerging concern

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ABSTRACT

Toxicological risk assessment of contaminants of emerging concern (CEC) in (sources of) drinking water is required to identify potential health risks and prioritize chemicals for abatement or monitoring. In such assessments, concentrations of chemicals in drinking water or sources are compared to either (i) health-based (statutory) drinking water guideline values, (ii) provisional guideline values based on recent toxicity data in absence of drinking water guidelines, or (iii) generic drinking water target values in absence of toxicity data. Here, we performed a toxicological risk assessment for 163 CEC that were selected as relevant for drinking water. This relevance was based on their presence in drinking water and/or groundwater and surface water sources in downstream parts of the Rhine and Meuse, in combination with concentration levels and physico-chemical properties. Statutory and provisional drinking water guideline values could be derived from publically available toxicological information for 142 of the CEC. Based on measured concentrations it was concluded that the majority of substances do not occur in concentrations which individually pose an appreciable human health risk. A health concern could however not be excluded for vinylchloride, trichloroethene, bromodichloromethane, aniline, phenol, 2-chlorobenzenamine, mevinphos, 1,4-dioxane, and nitrolotriacetic acid. For part of the selected substances, toxicological risk assessment for drinking water could not be performed since either toxicity data (hazard) or drinking water concentrations (exposure) were lacking. In absence of toxicity data, the Threshold of Toxicological Concern (TTC) approach can be applied for screening level risk assessment. The toxicological information on the selected substances was used to evaluate whether drinking water target values based on existing TTC levels are sufficiently protective for drinking water relevant CEC. Generic drinking water target levels of 37 μg/L for Cramer class I substances and 4 μg/L for Cramer class III substances in drinking water were derived based on these CEC. These levels are in line with previously reported generic drinking water target levels based on original TTC values and are shown to be protective for health effects of the majority of contaminants of emerging concern evaluated in the present study. Since the human health impact of many chemicals appearing in the water cycle has been studied insufficiently, generic drinking water target levels are useful for early warning and prioritization of CEC with unknown toxicity in drinking water and its sources for future monitoring.

## 1. Introduction

Due to population and economic growth, the rapidly intensifying production and use of chemicals (Bernhardt et al., 2017), longer periods of reduced river discharge as a consequence of climate change (Sjerps et al., 2017), and improved sensitivity of analytical techniques, the number of chemicals that is detected in the aquatic environment is rapidly increasing (Sjerps et al., 2016). For a number of chemicals known to reach drinking water, statutory standards are in place that are in part based on toxicological data. For most chemicals present in surface and groundwater, however, statutory standards, drinking water guideline levels derived by acknowledged international institutes in the area of human health protection, or provisional guideline values based on toxicological information have not been reported. The lack of insight

*Abbreviations:* ADI, Acceptable Daily Intake; BMD, Benchmark dose; BQ, Benchmark Quotient; CMR, carcinogenic, mutagenic, or toxic to reproduction; CEC, contaminants of emerging concern; DNEL, Derived No Effect Level; GLV, guideline value; LO(A)EL, Lowest Observed (Adverse) Effect Level; NO(A)EL, No Observed (Adverse) Effect Level; pGLV, provisional drinking water guideline value; RfD, Reference Dose; TTC, Threshold of Toxicological Concern; TDI, Tolerable Daily Intake; VSD, Virtually Safe Dose

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into the human health relevance of many chemicals appearing in the water cycle is a growing concern for drinking water utilities. We therefore compiled existing statutory guidelines and derived provisional health-based drinking water guidelines based on the most recent toxicity data available for selected drinking water relevant contaminants. These guidelines were used for health risk assessment of the individual substances. Exceedance of these guideline values indicates that collection of toxicological and occurrence data, when incomplete, and/or risk management measures are warranted. Deriving substance-specific guideline values is however labour intensive and publically available toxicity studies are often absent or incomplete for contaminants of emerging concern (CEC). For such chemicals, the concept of the Threshold of Toxicological Concern (TTC) can be used as an alternative approach to estimate the potential human health impact of drinking water exposure (Mons et al., 2013) and prioritize chemicals for further toxicological evaluation and future monitoring.

The TTC is a pragmatic approach, providing conservative generic exposure limits based on information on chemical structure and toxicological information on related chemicals. The concept originates from the Threshold of Regulation (ToR) that was based on carcinogenicity data for hundreds of chemicals (Rulis, 1986). In 2004, a TTC threshold level specifically designed for carcinogens with a structural alert for genotoxicity was introduced (Kroes et al., 2004). In addition, TTC levels have been calculated for groups of non-genotoxic chemicals, based on No Observed Adverse Effect (NO(A)EL) values derived from animal experiments (oral dosing) on (sub)chronic, reproductive and developmental toxicity. Using the Cramer decision tree, 613 non-carcinogenic chemicals (covering industrial chemicals, pharmaceuticals, food substances, and environmental, agricultural and consumer chemicals) were assigned to Cramer classes I, II or III, based on their functional group with the greatest potential toxicity (Munro et al., 1996). For each class, the 5th percentile of the NO(A)EL data was chosen as a cut-off exposure level. Subsequent application of an uncertainty factor of 100 accounting for inter- and intraspecies differences and a default adult body weight of 60 kg resulted in TTCs representing exposure levels at which a 95% chance exists that any chemical belonging to the same class does not elicit adverse human health effects. Kroes et al. (2004) finally introduced a separate threshold for certain neurotoxicants and pesticides (i.e. organophosphates and carbamates), since this endpoint would not be sufficiently covered by the threshold for Cramer class III compounds. Since each chemical can be categorized in one of the groups of chemicals for which TTC values have been derived, little practical value remains for the ToR (EFSA/WHO, 2016). Several studies evaluated the representativeness of the TTC values for extended or alternative groups of substances (Supplementary data I provides an overview). Compared to the original TTCs derived by Munro et al. (1996), in general, quite similar thresholds were calculated (Fig. 1). This indicates that the TTCs are sufficiently protective against potential health hazards of a wide range of chemicals, as was also concluded by EFSA (2012a).

The TTC approach should not be applied to substances with complex chemical structures having multiple structural elements and highly unique structures, such as some pharmaceuticals (SCCS, 2012). Other substances that are excluded from the TTC approach, either due to underrepresentation in the databases or because they may still be of toxicological concern at the TTC exposure levels, include high potency carcinogens (i.e. aflatoxin-like, azoxy- or *N*-nitroso-compounds, benzidines, hydrazines), inorganic substances, metals and organometallics, proteins, steroids, organosilicon compounds, chemicals that are known or predicted to bioaccumulate, nanomaterials, radioactive substances, and mixtures of substances containing unknown chemical structures (Kroes et al., 2004; EFSA, 2012a; EFSA/WHO, 2016).

The TTC concept is nowadays used to prioritize chemicals that may be of health concern in regulatory settings for packaging materials, food and feed additives including flavouring substances, metabolites of pesticides, and pharmaceuticals (Hennes, 2012; EC, 2000a, 2000b;

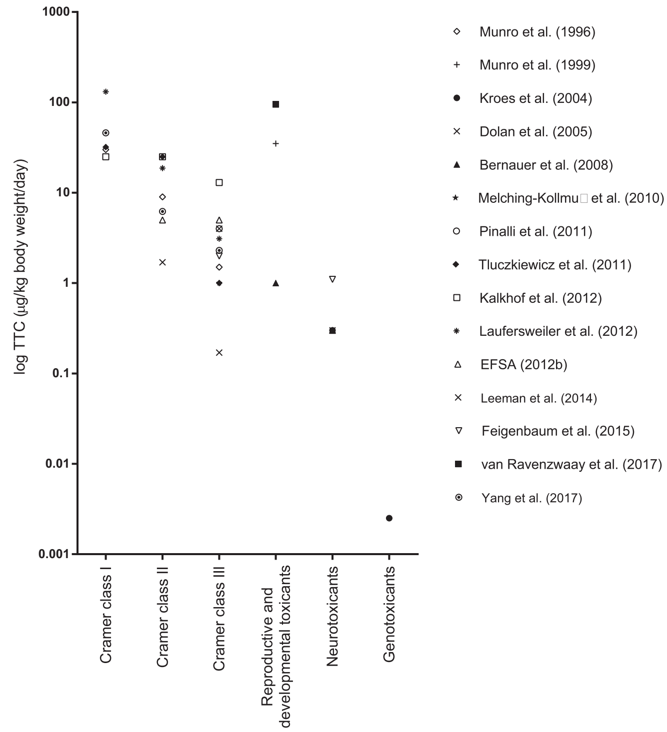


**Fig. 1.** Comparison of published TTC values (Cramer et al., 1978; Dewhurst and Renwick, 2013; Dolan et al., 2005; Feigenbaum et al., 2015; Kalkhof et al., 2012; Laufersweiler et al., 2012; Munro et al., 1999; URL1, n.d; URL2, n.d; Van Ravenzwaay et al., 2017 and Yang et al., 2017).

EFSA, 2012a, 2012b). A number of studies have been published in which generic drinking water target levels for organic contaminants have been derived from the original TTC values (Table 1). Such generic target levels are intended as an early warning tool that allows screening level risk assessment of drinking water contaminants for which standards or guideline values and toxicity data are lacking.

All of the studies in Table 1 used the original toxicity dataset of Munro et al. (1996); none calculated drinking water target levels using a toxicity dataset for actual drinking water contaminants, which form a subset of generally water-soluble, mobile, and persistent chemicals. Chemicals in the dataset of Munro et al. (1996) have a log$K_{ow}$ up to 15.3 (Health Canada, 2016), while the log$K_{ow}$ of chemicals ending up in drinking water is usually below 4 (Sjerps et al., 2016). To evaluate whether the existing TTC levels are applicable for risk assessment of substances without toxicity data occurring in drinking water and its sources, we derived generic exposure thresholds and drinking water target levels based on toxicity data gathered for the CEC for drinking water and the TTC methodology. The results were compared to previously published TTC levels and drinking water target levels derived from them. In order to assess whether the calculated generic drinking water target levels were sufficiently protective for health effects of CEC, they were compared to the (provisional) drinking water guideline values which we derived for 142 chemicals and related to the detected concentration levels of these drinking water contaminants.

## 2. Materials and methods

### *2.1. Selection of substances*

Chemical contaminants detected in drinking water, raw water (collected water before further treatment), and various drinking water sources (i.e. surface water from the river Rhine and Meuse and groundwater) were retrieved from the restricted REWAB (Registration tool Water Quality Data) database. This database collects monitoring