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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; 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.

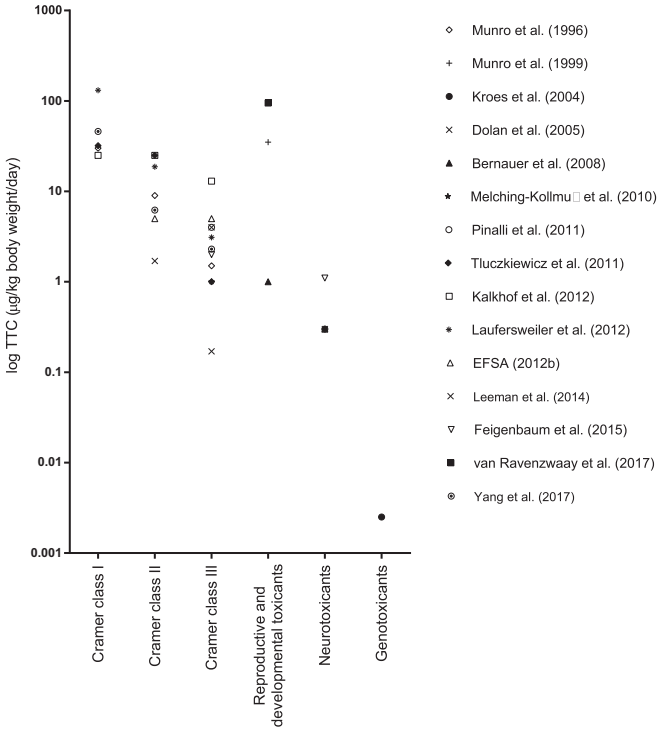

Fig. 1. Comparison of published TTC values (Cramer et al., 1978; Dewhurst and Renwick, 2013; Dolan et al., 2005; Feigenbaum et al., 2015; Kalkhof et al., 2012; Laufersweiler et al., 2012; Munro et al., 1999; URL1, n.d; URL2, n.d; Van Ravenzwaay et al., 2017 and Yang et al., 2017).

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

Table 1
Published generic drinking water target levels based on TTC values.

Classification	TTC (μg/day)	Allocation to drinking water (%)	Consumption (L/day)	Drinking water target level (μg/L)	Reference
Cramer class I	1800	100	2	900	Brüschweiler (2010)
		20	2	180	Etchepare and van der Hoek (2015)
		≥0.5	2	≥4.5	Dieter (2014)
Cramer class II	540	100	2	270	Brüschweiler (2010)
		≥1.7	2	≥4.5	Dieter (2014)
Cramer class III	90	100	2	45	Brüschweiler (2010)
		20	2	9	Etchepare and van der Hoek (2015)
		10	2	4.5	Dieter (2014)
		10	2	4.5	Laabs et al. (2015)
	60[a]	10	2	3[b]	Melching-Kollmuß et al. (2010)
Organophosphates and carbamates	18	100	2	9	Brüschweiler (2010)
		10	2	0.9	Dieter (2014)
Carcinogens (ToR)	1.5[c]	100	2	0.75	Brüschweiler (2010)[d]
		100	2	0.75	EC (2000b)
		10	2	0.1	Mons et al. (2013)[d]
		10	2	0.075	Dieter (2014)[d]
Genotoxic substances	0.15	?	?	0.15[e]	Etchepare and van der Hoek (2015)
		100	2	0.075	Brüschweiler (2010)
		100	2	0.075	Dieter (2014)
		10	2	0.01	Mons et al. (2013)
Steroid hormones	–	–	–	0.01	Mons et al. (2013)[f]

[a] Adapted TTC value based on reprotoxic and developmental endpoints as summarized by Bernauer et al. (2008) based on an uncertainty factor of 1000 instead of 100 due to a limited data set.

[b] Proposed to be applied to non-relevant metabolites of plant protection products.

[c] The ToR is no longer supported as a TTC class by EFSA (2012a) and EFSA/WHO (2016). Instead, non-gentoxic carcinogens can be classified into the corresponding Cramer classes.

[d] Only applies to non-genotoxic substances.

[e] A drinking water target level of 0.15 μg/L was reported by Etchepare and van der Hoek (2015); however, the assumption of 2 L of drinking water consumption per day and 20% allocation of exposure to drinking water which the authors claimed to have used should have resulted in a target level of 0.015 μg/L.

[f] As steroid hormone compounds are abundantly found in surface water and are thus of concern for drinking water quality, Mons et al. (2013) included these compounds in the list of proposed target levels, despite the opinion of EFSA (2012a, 2012b) to exclude them from the TTC approach.

results of the Dutch drinking water companies, i.e. mean and maximum per parameter per production station per year in raw and distributed water, and comprises over 80.000 data points per year for the statutory chemical parameters. In addition, the database of the association of river waterworks (RIWA) was used to include organic compounds monitored in Dutch surface waters (approximately 130 measurements per compound per year). Besides, project-based and non-routine monitoring results of the Dutch drinking water laboratories (Vitens, HWL, WLN and Aqualab Zuid) and Rijkswaterstaat (Dutch department of public works and water management) were included. Data gathered in research projects performed for the Joint Research Program of the Dutch water companies (BTO) and by Royal Haskoning (Royal Haskoning, 2014; measurements from 106 locations) were added to the data set. In most data sources, selection criteria were applied regarding minimally detected concentrations or frequencies with which substances were detected. Only mean and/or maximum concentrations were reported and used in the present evaluation. The number of measurements on which these values were based differs per compound and water type. When multiple sources reported measured concentrations, the highest value was used.

Collected chemicals were evaluated using the flow diagram as presented in Fig. 2. Substances were prioritized when they were either (i) present in drinking water, (ii) present in raw (untreated) water at a concentration above the drinking water target levels based on TTC values reported by Mons et al. (2013; Table 1), or (iii) present in direct drinking water sources (i.e. surface waters used for drinking water abstraction), relatively hydrophilic (octanol/water partition coefficient $\log K_{OW} < 4$), non-volatile (Henry's Law constant $K_iH(w) < 0.02$), and detected at a concentration above the target levels reported by Mons et al. (2013). Substances were labeled as carcinogenic, mutagenic, or toxic to reproduction (CMR) when the International Agency for Research on Cancer (IARC) classified them as (probably) carcinogenic to humans (category 1 or 2A) (URL1) and/or they are present on the list of carcinogenic substances and processes published by the Dutch Ministry of Social Affairs and Employment, which includes all substances and processes included in Annex VI of Regulation (EC) No 1272/2008 and Annex I of Directive 2004/37/EC and substances categorized as carcinogenic by the Health Council of the Netherlands (URL2). These classifications were included in the prioritization in order to apply the appropriate drinking water target level based on TTC values, and since CMR substances may cause permanent adverse health effects when exposure thresholds are exceeded even for a short time period. Substances that were detected in miscellaneous surface or groundwater (not being a direct drinking water source), and not reported in the other water types did not qualify for further health risk assessment. In case these substances were hydrophilic, non-volatile, and CMR-positive and occurred in concentrations above the target levels reported by Mons et al. (2013), they were considered for future monitoring. Removal efficiencies during drinking water treatment processes were not taken into account in the prioritization.

2.2. Toxicological risk assessment

Reported (statutory) drinking water guideline values and underlying toxicity data were retrieved from the World Health Organization (WHO), U.S. Environmental Protection Agency (EPA), Californian Office of Environmental Health Hazard Assessment (OEHHA), Health Canada, The Australian National Health and Medical Research Council (NHMRC), Danish EPA, and the Dutch Drinking Water Directive and the Ministerial Regulation materials and chemicals drinking water- and

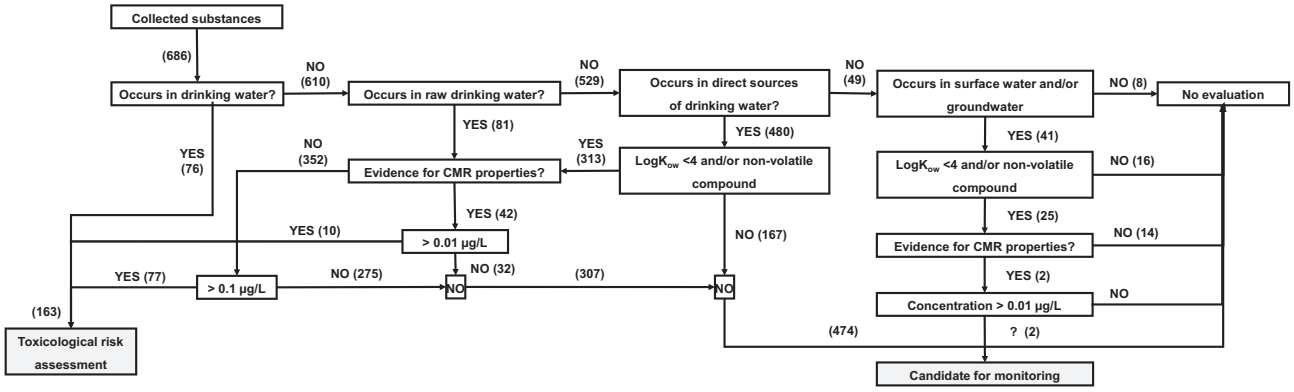

Fig. 2. Flow diagram for selection of drinking water relevant substances for toxicological risk assessment. Numbers between brackets indicate numbers of substances. 'NO' indicates that substances were not measured in a specific water type, either because they were not detected above the detection limit or monitoring data were not available.

warm tap water supply. When no health-based guideline values were reported, provisional drinking water guideline values were calculated based on either Tolerable Daily Intake (TDI), Acceptable Daily Intake (ADI), Reference Dose (RfD), Derived No Effect Level (DNEL), or oral doses or drinking water concentrations corresponding to a specified extra life time cancer risk. When acceptable intake levels were absent, NO(A)EL, Lowest Observed (Adverse) Effect Level (LO(A)EL) or Benchmark dose (BMD) level, or alternative information on health effects were used. All toxicological information was retrieved by online search in the following data sources, respectively:

i. Documents supporting regulatory drinking water guideline levels, when available;
ii. TERA (Toxicology Excellence for Risk Assessment) International Toxicity Estimates for Risk (ITER) Database including toxicological evaluations by the WHO International Programme on Chemical Safety (IPCS), U.S. EPA, Agency for Toxic Substances and Disease Registry (ATSDR), Health Canada, and the Dutch National Institute for Public Health and the Environment (RIVM);
iii. The Organisation for Economic Co-operation and Development (OECD) eChemPortal linking to additional information sources such as the OECD Existing Chemicals Screening Information Data Sets (SIDS), Chemical Safety Information from Intergovernmental Organizations (INCHEM), and the Database by the Hazardous Substances Data Bank (HSDB);
iv. Toxicological evaluations performed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Joint FAO/WHO Meeting on Pesticide Residues (JMPR), U.S. EPA, European Food Safety Authority (EFSA), EC Scientific Committee on Food (SCF), European Chemicals Agency (ECHA), European Medicines Agency (EMA), and the RIVM;
v. The lowest therapeutic dose (LTD) reported in the Dutch Farmacotherapeutic Compass or by the Medicines Evaluation Board (CBG) or the WHO Defined Daily Dose (DDD) were used as NOAEL value for pharmaceuticals, to which an uncertainty factor of 100 was applied to derive the acceptable daily intake, in case this was not reported in the other information sources;
vi. Peer reviewed literature in case no (more recent) data were available in the aforementioned sources.

When multiple health based exposure thresholds were reported, the most conservative value was used. For substances that were concluded to be (suspected) genotoxic carcinogens by the consulted authorities, all acceptable exposure levels were converted to 10^{-6} additional life time cancer risk levels.

Provisional drinking water guideline values (pGLV) were calculated for substances for which no health-based drinking water guidelines were previously reported. For threshold chemicals formula (I) was used, which takes contribution (by default 80%) of other sources than drinking water to the total exposure level into account. For non-threshold (genotoxic) chemicals, drinking-water guideline values specify a concentration associated with a defined excess lifetime cancer risk derived by linear extrapolation. Virtually Safe Doses (VSD) corresponding to a 10^{-6} risk level were translated into drinking water concentrations using formula (II) (WHO, 2011):

I. pGLV (µg/L) = [TDI, ADI, RfD, or DNEL (µg/kg bw/day) × 60 kg body weight × 20% drinking water allocation] / 2 L drinking water consumption;
II. pGLV (µg/L) = [10^{-6} extra life time cancer risk level × 60 kg body weight] / 2 L drinking water consumption.

Similar to the strategy applied by Schriks et al. (2010), substances were categorized according to the confidence level of the drinking water guideline value: (A) representing compounds with a statutory drinking water guideline value, (B) representing compounds with an established ADI, RfD, TDI etc., (C) representing compounds for which the TDI was calculated with an established LO(A)EL or NO(A)EL and (D) representing compounds for which the TDI was calculated based on miscellaneous toxicological information.

Finally, the so-called Benchmark Quotient (BQ) was calculated as the ratio between the mean or maximum reported drinking water concentration and the (p)GLV. A BQ value of 1 represents a (drinking) water concentration equal to the (provisional) guideline value. A BQ value of ≥1 in drinking water may thus be of potential human health concern if the water were to be consumed over a lifetime period. Compounds with a BQ value ≥0.1 in drinking may warrant further investigation. For compounds detected in raw water, surface water and groundwater, drinking water treatment may provide additional safety. For these substances it was presumed that a BQ of ≤0.2 presents absence of appreciable concern for a risk to human health (Schriks et al., 2010).

2.3. Calculation of TTC levels

First, a categorization of the collected substances into compounds with predicted genotoxicity and structural characteristics corresponding to Cramer class I, II or III was performed. Only substances that had been demonstrated to be genotoxic or were concluded to be potentially genotoxic based on their toxicological evaluation (and for which lifetime additional cancer risk values had thus been reported) were classified as genotoxic substances. High potency carcinogens were excluded from the TTC calculation. SMILES codes of the remaining substances were loaded in Toxtree v2.6.13 and the 'Cramer rules with

Table 2
Statutory and provisional drinking water guideline values for contaminants of emerging concern in drinking water and its sources.

CAS	Name	TDI or VSD (μg/kg bw)[a]	Source[b]	Health-based (p)GLV (μg/L)[a]	Nr. in Fig. 3
Category A compounds					
75-01-4	**Ethene, chloro-[vinyl chloride]**	0.001	WHO (VSD)	0.03	***1***
79-01-6	**Ethene, trichloro-**	0.014	U.S. EPA (VSD)	0.5	***2***
75-27-4	**Methane, bromodichloro-**	0.07	WHO (VSD)	2.1	***3***
60-00-4	**Ethylenediaminetetraacetic acid [EDTA]**	190	Australian NHMRC	250	***4***
79-43-6	Acetic acid, dichloro-	0.133	WHO (VSD)	4	*5*
107-06-2	**Ethane, 1,2-dichloro-**	0.1	WHO (VSD)	3	***6***
78-87-5	Propane, 1,2-dichloro-	14	WHO	5	*7*
62-53-3	**Benzenamine [aniline]**	1.44	RIVM	10.08	***8***
1634-04-4	**Ether, methyl *tert*-butyl [MTBE]**	0.557	OEHHA (VSD)	13	***9***
124-48-1	Methane, dibromochloro-	21.4	WHO	100	*10*
75-25-2	Methane, tribromo-[bromoform]	17.9	WHO	100	*11*
127-18-4	**Ethene, tetrachloro-**	14	WHO	40	***12***
7085-19-0	Mecoprop (racemate)	3.33	WHO	10	*13*
75-09-2	Methane, dichloro-	6	WHO	20	*14*
5915-41-3	Terbutylazine [TBA}	2.2	WHO	7	*15*
67-66-3	Methane, trichloro-[chloroform]	15	WHO	300	*16*
93-65-2	Propanoic acid, 2-(4-chloro-2-methylphenoxy)-	3.33	WHO	10	*17*
120-82-1	Benzene, 1,2,4-trichloro-	7.7	WHO	20	*18*
34123-59-6	Isoproturon	3	WHO	9	*19*
314-40-9	2.4(1H,3H)-Pyrimidinedione, 5-bromo-6-methyl-3-(1-methylpropyl)-[bromacil]	100	U.S. EPA	70	*20*
100-42-5	Benzene, ethenyl-[styrene]	97.1	WHO	20	*21*
106-42-3	Benzene, 1.4-dimethyl-	179	WHO	500	*22*
108-38-3	Benzene, 1,3-dimethyl-	179	WHO	500	*23*
108-88-3	Benzene, methyl-[toluene]	223	WHO	700	*24*
1071-83-6	Glycine, *N*-(phosphonomethyl)-[glyphosate]	1750	U.S. EPA	700	*25*
78-40-0	Phosphoric acid, triethyl ester	560	Schriks et al., 2010	375	*26*
71-55-6	Ethane, 1,1,1-trichloro-	600	WHO	2000	*27*
94-74-6	Acetic acid, (4-chloro-2-methylphenoxy)-[MCPA]	0.5	WHO	2	*28*
108-95-2	**Phenol**	0.04	ITER	0.28	***29***
95-51-2	**Benzenamine, 2-chloro-**	0.009	RIVM (VSD)	0.27	***30***
156-59-2	Ethene, 1,2-dichloro-,(*Z*)-	17	WHO	50	*31*
76-03-9	Acetic acid, trichloro-	32.5	WHO	200	*32*
23135-22-0	Oxamyl	20	Australian NHMRC	7	*33*
123-91-1	**1.4-Dioxane**	0.01	U.S. EPA (VSD)	0.35	***34***
139-13-9	**Glycine, *N,N*-bis(carboxymethyl)-[nitrolotriacetic acid]**	10	WHO	200	***35***
79-11-8	Acetic acid, chloro-	3.5	WHO	20	*36*
100-97-0	Hexamine [urotropin]	150	Schriks et al., 2010	750	*37*
75-35-4	Ethene, 1,1-dichloro-	46	WHO	140	
62-75-9	Methanamine, *N*-methyl-*N*-nitroso-[NDMA]	0.00002	U.S. EPA (VSD)	0.0007	
Category B compounds					
330-54-1	Diuron	0.057	USGS (VSD)	2	*38*
10605-21-7	Carbendazim	0.419	U.S. EPA (VSD)	13.4	*39*
143-24-8	**2,5,8,11,14-Pentaoxapentadecane [tetraglyme]**	1	ECHA	7	***40***
57-68-1	Sulfadimidine	4	JECFA	28	*41*
91-20-3	Naphthalene	20	ITER	140	*42*
22071-15-4	Ketoprofen	5	EMA	35	*43*
6339-19-1	Desphenylchloridazon	100	EFSA	700	*44*
2008-58-4	2.6-Dichlorobenzamide	50	EFSA	350	*45*
122-34-9	Simazine	5	ITER	35	*46*
882-09-7	Clofibric acid	10	RIVM	70	*47*
55297-95-5	Tiamulin	30	EMA	210	*48*
25057-89-0	Bentazone	30	U.S. EPA	210	*49*
298-46-4	Carbamazepine	16	RIVM	112	*50*
109-99-9	Furan, tetrahydro-	900	ITER	6300	*51*
51218-45-2	Metolachlor	100	EFSA	700	*52*
103-90-2	Acetamide, *N*-(4-hydroxyphenyl)-	50	EMA	350	*53*
126-73-8	Phosphoric acid tributyl ester	80	ITER	560	*54*
111-96-6	Ethane, 1,1-oxybis[2-methoxy-[diglyme]	1040	ECHA	7280	*55*
1698-60-8	Chloridazon	100	EFSA	700	*56*
134-62-3	Diethyl toluamide [DEET]	750	RIVM	5250	*57*
120-12-7	Anthracene	300	ITER	2100	*58*
112-49-2	2,5,8,11-Tetraoxadodecane [triglyme]	3130	ECHA	21910	*59*
29878-31-7	1H-Benzotriazole, 4-methyl-	6.7	Danish EPA	46.9	*60*
2634-33-5	1.2-Benzisothiazol-3(2H)-one	15	EFSA	105	*61*
163515-14-8	Dimethenamid-P	20	RIVM	140	*62*
13674-84-5	2-Propanol, 1-chloro-,phosphate (3:1)	520	ECHA	3640	*63*
95-14-7	1H-Benzotriazole	540	ECHA	3780	*64*
338-45-4	**Mevinphos, trans-isomer**	0.8	JMPR	5.6	***65***
15307-86-5	Diclofenac	0.5	EMA	3.5	*66*
156-60-5	Ethene, 1,2-dichloro-,(E)-	20	ITER	140	*67*
79-00-5	Ethane. 1,1,2-trichloro-	4	IRIS	28	*68*

(*continued on next page*)

Table 2 (*continued*)

CAS	Name	TDI or VSD (μg/kg bw)[a]	Source[b]	Health-based (p)GLV (μg/L)[a]	Nr. in Fig. 3
63-25-2	Carbaryl	7.5	EFSA	52.5	*69*
34681-23-7	Butoxycarboxim	1.29	RIVM	9.03	*70*
2593-15-9	Ethazole	15	EFSA	105	*71*
84-66-2	Diethyl phthalate	200	RIVM	1400	*72*
102-06-7	Guanidine, *N*,*N*-diphenyl-	85	ECHA	595	*73*
126-71-6	Phosphoric acid, tris(2-methylpropyl) ester	2130	ECHA	14910	*74*
34681-10-2	Butocarboxim	20	RIVM	140	*75*
99105-77-8	Sulcotrione	0.4	EFSA	2.8	*76*
149-30-4	2(3H)-Benzothiazolethione	1.29	RIVM	9.03	*77*
120-78-5	Benzothiazole, 2,2-dithiobis-	94	RIVM	658	*78*
55589-62-3	Acesulfame-K	9000	EU SCF	63000	*79*
56038-13-2	Sucralose	15000	EFSA	105000	*80*
29385-43-1	1H-Benzotriazole, 4(or 5)-methyl-	1.29	RIVM	9.03	*81*
67-64-1	Acetone	900	EFSA	6300	*82*
39184-27-5	Thiofanox sulfoxide	0.3	RIVM	2.1	*83*
54-31-9	Furosemide	2.5	EMA	17.5	*84*
50-78-2	Aspirin	8.3	RIVM	58.1	*85*
330-55-2	Linuron	3	EFSA	21	*86*
67-43-6	Glycine,*N*,*N*-bis 2-bis(carboxymethyl)amino ethyl-	900	ECHA	6300	*87*
106-47-8	Benzenamine,4-chloro-	2	ITER	14	*88*
15972-60-8	Alachlor	10	ITER	70	*89*
58-93-5	Hydrochlorothiazide	25	EMA	175	*90*
107534-96-3	Tebuconazole	30	EFSA	210	*91*
133-07-3	Folpet	100	EFSA	700	*92*
24579-73-5	Propamocarb	244	EFSA	1708	*93*
304-55-2	Butanedioic acid. 2.3-dimercapto-,(*R**,*S**)-	300	RIVM	2100	*94*
109-87-5	Methane,dimethoxy-	18100	ECHA	126700	*95*
111991-09-4	Nicosulfuron	2000	EFSA	14000	*96*
1918-16-7	Propachlor	13	ITER	91	
95-50-1	Benzene,1.2-dichloro-	90	ITER	630	
96-18-4	Propane,1.2.3-trichloro-	0.00033	ITER (VSD)	0.010	
67-72-1	Ethane,hexachloro-	0.025	U.S. EPA (VSD)	0.9	
148-79-8	Thiabendazole	100	EFSA	700	
110488-70-5	Dimethomorph	50	EFSA	350	
205939-58-8	Dimethenamid ESA	20	EFSA	140	
187022-11-3	Acetochlor ESA sodium salt	3.6	EFSA	25.2	
Category C compounds					
791-28-6	Phosphine oxide,triphenyl-[TPPO]	8	Schriks et al., 2010	56	*97*
52508-35-7	Dikegulac sodium	700	HSDB	4900	*98*
17254-80-7	Desphenylchloridazon,methyl-	50	EFSA	350	*99*
74-95-3	Methane,dibromo-	300	OECD	2100	*100*
1066-51-9	Aminomethylphosphonic acid [AMPA]	300	Schriks et al., 2010	2100	*101*
122-88-3	Acetic acid,(4-chlorophenoxy)-	15	HSDB	105	*102*
Category D compounds					
25812-30-0	Gemfibrozil	1.5	Farm. kompas	10.5	*103*
525-66-6	Propranol	3.3	Farm. kompas	23.1	*104*
57-62-5	Chlortetracycline	3	JECFA	21	*105*
49562-28-9	Fenofibrate	16.6	RIVM	116.2	*106*
60-80-0	Phenazone	41.6	RIVM	291.2	*107*
479-92-5	Propyphenazone	25	Farm. kompas	175	*108*
125-33-7	Primidone	125	Farm. kompas	875	*109*
58-08-2	Caffeine	5700	EFSA	39900	*110*
117-96-4	Benzoic acid. 3,5-bis(acetylamino)-2,4,6-triiodo-[amidotrizoic acid]	85300	RIVM	597100	*111*
62883-00-5	Iopamidol	118600	RIVM	830200	*112*
37350-58-6	Metoprolol	2.8	RIVM	19.6	*113*
83-15-8	4-Acetamidoantipyrin	10	EMA	70	*114*
36507-30-9	Carbamazepine 10,11-epoxide	16	RIVM	112	*115*
604-75-1	Oxazepam	2.5	Farm. kompas	17.5	*116*
1646-87-3	Aldicarb sulfoxide	3	EFSA	21	*117*
108-20-3	Propane,2.2-oxybis-	200	RIVM	1400	*118*
73334-07-3	Iopromide	83333	RIVM	583331	*119*
78649-41-9	Iomeprol	291600	CBG	2041200	*120*
66108-95-0	Iohexol	125000	RIVM	875000	*121*
61-33-6	Pencillin G	20.8	WRF	145.6	*122*
45951-45-9	Sulfamic acid,*N*-cyclohexyl-	7000	EU SCF	49000	*123*
631-64-1	Acetic acid,dibromo-	3.33	Farm. kompas	23.31	*124*
58-55-9	Theophylline	1.66	Farm. kompas	11.62	*125*
61869-08-7	Paroxetine	3.33	Farm. kompas	23.31	*126*
657-24-9	Metformin	56	RIVM	392	*127*
69-72-7	Benzoic acid,2-hydroxy-	8.3	EMA	58.1	*128*
13429-07-7	2-Propanol,1-(2-methoxypropoxy)-	200	OECD	1400	*129*
61-56-3	Sulthiame	4000	WHO	28000	*130*
27203-92-5	Tramadol	8.3	Farm. kompas	58.1	*131*

(*continued on next page*)

Table 2 (*continued*)

CAS	Name	TDI or VSD (μg/kg bw)[a]	Source[b]	Health-based (p)GLV (μg/L)[a]	Nr. in Fig. 3
15045-43-9	2,2,5,5-Tetramethyl-tetrahydrofuran	1	RIVM	7	

[a] Detailed information on the derivation of NOAEL, TDI/VSD, and (p)GLV levels can be found in Supplementary data III. For (suspected) genotoxic carcinogens, the VSD corresponding to a 10^{-6} cancer risk level is indicated. (p)GLV = (provisional) drinking water guideline value.

[b] For abbreviations see Section 2.2. Chemicals for which measured concentrations were available are numbered and presented in Fig. 3; when BQ values > 0.1 in drinking water or > 0.2 were calculated in raw water and/or direct sources, chemicals are printed in bold.

extensions' were applied. Similarly to Munro et al. (1996), organophosphates and carbamates were not classified separately. The NO(A)EL, LO(A)EL, BMDL, or life time additional cancer risk levels on which the most conservative exposure thresholds retrieved in the toxicological risk assessment (see Section 2.2) were based, were collected for all chemicals. The following corrections to these toxicity data were applied when necessary:

- For NO(A)EL or BMD levels that were derived from subchronic toxicity studies, an assessment factor of 3 was applied to convert them to chronic exposure, similar to the approach of Munro et al. (1996);
- When only LO(A)EL values were available, these levels were divided by a default value of 7 (ECHA, 2012);
- When human toxicity data were reported, NO(A)EL or LO(A)EL values were multiplied by 10, because later on an uncertainty factor of 10 for interspecies variation would be applied to the 5th percentile of the data to derive a TTC threshold values;
- When cancer risk levels were expressed in μg/L drinking water, they were transformed into a VSD representing a 10^{-6} excess lifetime cancer risk level using the drinking water consumption per day and the body weight by which the drinking water concentration was derived.

Since the number of substances categorized as (potential) genotoxicants and Cramer class II substances was very limited, a generic exposure threshold was not calculated for those chemicals. All (corrected) NO(A)EL values for Cramer class I and III substances were subjected to a lognormal conversion. First, this data set was added to the original Munro et al. (1996) data set to evaluate whether calculated TTC values would change significantly. Next, new generic exposure thresholds were calculated for each class by applying the TTC methodology using the (corrected) toxicity data. The data were checked for normal distribution using the Shapiro-Wilk test, 5th percentiles were derived, and confidence limits were estimated using the Wilson score interval with continuity correction assuming a binominal distribution for the cumulative data (Newcombe, 1998). Since this method only calculates the confidence interval of the *P*-value of a given measured value, the confidence interval for the measured value was calculated numerically using Excel. The 5th percentiles were multiplied by 60 kg body weight (similar to Munro et al., 1996) and an uncertainty factor of 100 was applied to the 5th percentile to account for interspecies and intraspecies differences. Finally, the resulting threshold values were converted to drinking water equivalent levels by applying a default drinking water allocation of 20% and dividing the values by 2 L of total consumed drinking water, similar to the pGLV calculation (WHO, 2011). The resulting generic drinking water target levels were subsequently compared to (i) the (provisional) drinking water guideline values and (ii) the concentrations of the contaminants detected in drinking water.

3. Results

3.1. Selection of contaminants

The total collected database consists of 1097 measured medium and maximum concentrations originating from 2010 until 2014 for 686 chemicals (see Supplementary data II). Of these chemicals, 76 had been detected in drinking water. The remaining chemicals were prioritized using the scheme presented in Fig. 2 (see also Supplementary data II), resulting in 87 substances with drinking water relevance detected in raw drinking water or direct sources. Of the substances present in groundwater or surface water, two were prioritized for further monitoring by the Dutch drinking water utilities: 2-nitroanisole, a contrast medium present in surface water, and benomyl, a plant protection product detected in waste water treatment effluent. Detected concentrations were not reported for these compounds.

3.2. Toxicological risk assessment

Supplementary data III presents the 163 selected substances with their toxicological information and (provisional) drinking water guideline values. For 39 category A substances (31 of which have an industrial origin), (statutory) drinking water guideline values had been published. In three cases these guideline values were not health based, and therefore replaced by a TDI-based pGLV. For two substances, the derivation of the health based guideline value was not reported and the NOAEL (later on used for TTC calculation) was thus derived from another data source. For 67 category B, 6 category C and 30 category D substances, toxicity data were collected to calculate pGLVs. All (provisional) drinking water guideline values are shown in Table 2. For the remaining 21 substances, no toxicity data were found and these compounds were not further evaluated.

In Fig. 3, reported mean and maximum concentrations in drinking water, raw water and/or direct sources are compared to the (provisional) drinking water guideline values for those substances for which both data were available. Fig. 3 shows that for the majority of the substances, BQ values are < 1 and also < 0.1 (drinking water) or < 0.2 (raw water and sources). In drinking water, three compounds were detected with a BQ > 1: vinylchloride both at the mean and maximum detected concentration and trichloroethene and bromodichloromethane at the maximum concentration. In addition, the maximum drinking water concentration of aniline resulted in a BQ value > 0.1. In raw water, vinylchloride shows a BQ much higher than 1. For maximum concentrations of tetrachloroethene and phenol, BQ values of > 1 were calculated as well. The BQ value for tetrachloroethene was < 0.1 in the drinking water data available. Drinking water concentrations for phenol were not reported. Bromodichloromethane, 1,2-dichloroethane, 2-chlorobenzenamine and mevinphos show BQ values of > 0.2 in raw water. The BQ of 1,2-dichloroethane did not exceed 0.1 in drinking water. In direct drinking water sources, a BQ value > 1 was calculated for 1,4-dioxane and tetraglyme, while EDTA, MTBE and nitrolotriacetic acid show BQ values of > 0.2 at maximum detected concentrations. For tetraglyme, EDTA and MTBE, drinking water concentrations were reported which all resulted in a BQ < 0.1. For 88 out of the 163 selected substances, health risk assessment for drinking water could not be performed since either toxicity data or drinking water concentrations were lacking (see Supplementary data III).

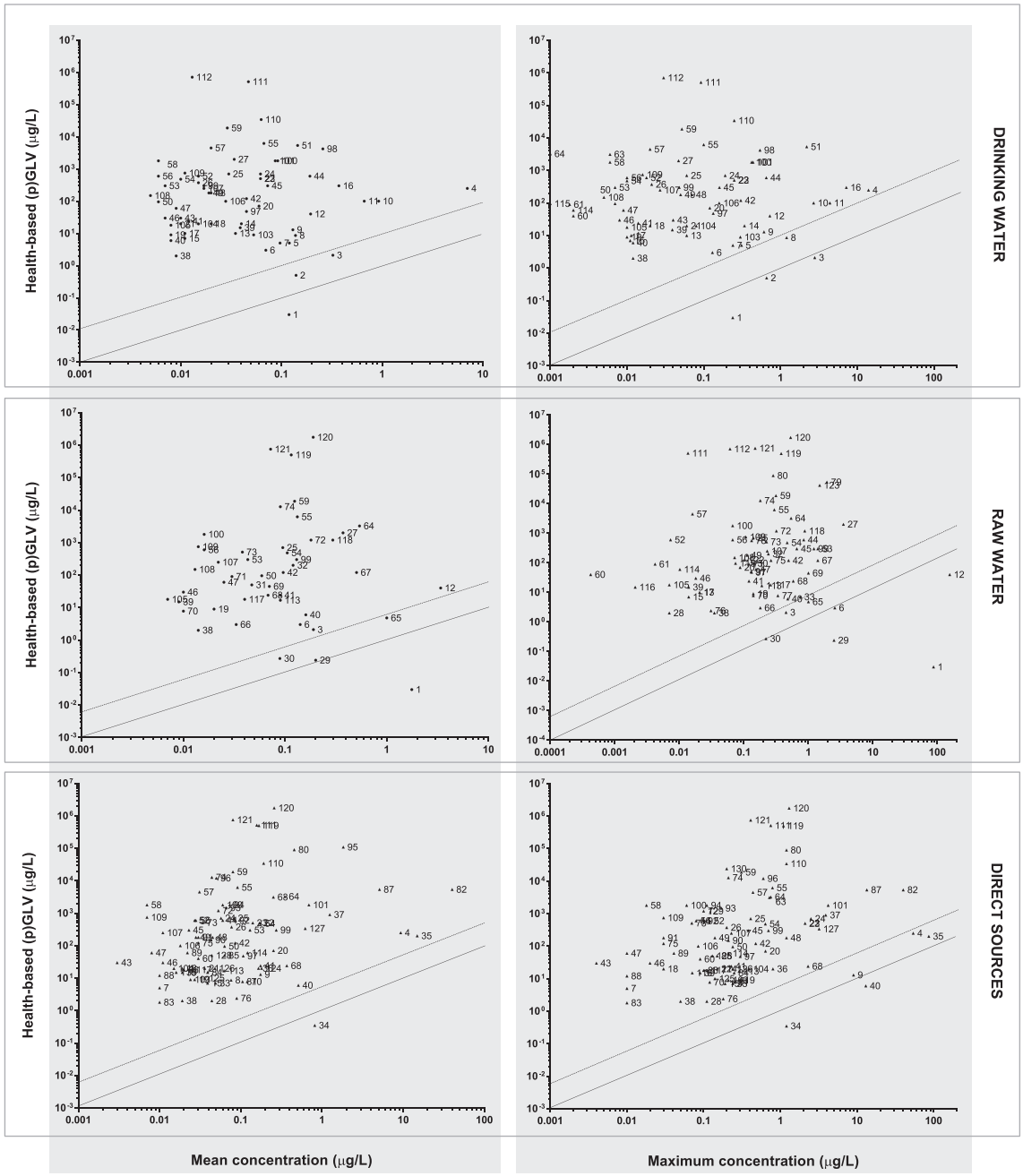

Fig. 3. Comparison of reported mean and maximal concentrations in drinking water, raw water, and direct sources to (provisional) drinking water guideline values [(p)GLVs]. A BQ of ≥1 (indicating potential human health concern at lifetime consumption) is calculated for chemicals below the continuous line, and a BQ of ≥0.1 (drinking water) or ≥0.2 (raw water and direct sources) (warranting further investigation) for substances below the dotted line. Numbers correspond to the substances presented in Table 2.

3.3. Calculation of TTC levels

Of the 163 selected substances with drinking water relevance, 57 are included in the original data sets that were used to derive the TTC values by Munro et al. (1996), Cheeseman et al. (1999) and Kroes et al. (2004) comprising a total of 1225 substances with CAS numbers (see Supplementary data III); these comprise 43 Cramer class III chemicals, 11 (potentially) genotoxic substances, and 3 Cramer class I chemicals. Toxtree classification shows that all but 3 of the 163 substances are categorized in one of the Cramer classes (Supplementary data III) with the majority ending up in Cramer class III, similar to the substances in the original TTC databases (Supplementary data I). Only two substances were placed in Cramer class II and 12 were classified as potential genotoxicants; a generic exposure threshold was not calculated for those chemicals. When the substances not yet included in the Munro et al. (1996) data set were added to Cramer class I and III, significantly lower TTC values of 26 and 1.3 µg/kg bw/day, respectively, were calculated (Supplementary data III). Fig. 4 shows the cumulative distributions of the lognormal converted NO(A)EL values of Cramer class I and III substances compared to the data from Munro et al. (1996). The geometric means of the NO(A)EL values for Cramer class I and III substances (third column in Table 3) were higher than those originally resulting from the Munro et al. (1996) analysis: NO(A)ELs for Cramer class I compounds ranged from 0.5 to 7203 mg/kg/day with a geometric mean of 112, and for class III NO(A)Els of 0.005–3775 mg/kg/day with a geometric mean of 9 were reported. The generic exposure

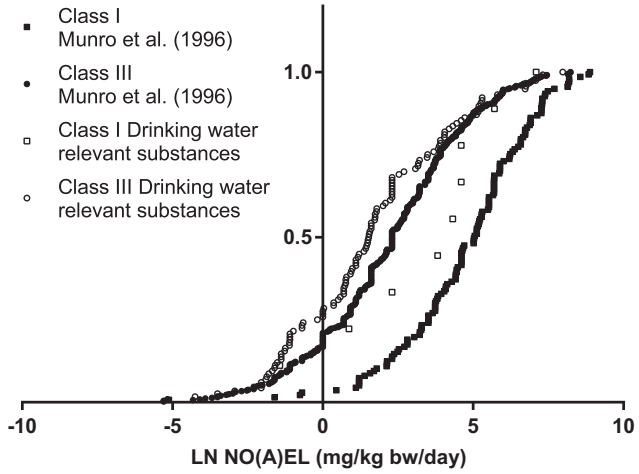

Fig. 4. Cumulative distributions of the lognormal converted NO(A)EL values for Cramer class I and Cramer class II substances compared to the NO(A)EL values used by Munro et al. (1996).

thresholds derived from the 5th percentile of NO(A)EL levels were however lower than those reported by Munro et al. (1996). The number of substances on which the Cramer class I exposure threshold is based are limited. Accordingly, the confidence interval of the 5th percentile, and thus of the derived generic exposure threshold, is somewhat larger than for the class III substances. The calculation of generic exposure thresholds and drinking water target levels for class I and class III is presented in Supplementary data III and summarized in Table 3.

To evaluate whether the calculated generic drinking water target levels (Table 3) are sufficiently protective for health effects of drinking water contaminants, they were compared to the substance-specific (p)GLVs (Table 2). In Cramer class I, (p)GLVs for styrene and tetraglyme were below the target level. In Cramer class III, (p)GLV for sulcotrione, diclofenac, thiofanox sulfoxide, MCPA and phenol were lower than the target level.

When the calculated generic drinking water target levels were compared to available monitoring data in drinking water (Table 3 and Supplementary data III), one of the class I substances (ATP) was reported to be present in a concentration above the target level. This was also the case for the class III substances bromoform, chloroform and EDTA. Their concentrations were however well below the substance-specific (p)GLVs.

4. Discussion

The present study illustrates that most of the currently detected drinking water relevant contaminants individually do not pose an appreciable human health risks. The same was concluded from earlier evaluations (Schriks et al., 2010; Bruce et al., 2010; De Jongh et al., 2012; Houtman et al., 2014). For a small number of chemicals, however, concentrations around or above the (p)GLV were reported. In drinking water, this indicates a potential health risk at lifelong exposure. All substances with a BQ value > 0.1 in drinking water as well as those with a BQ > 0.2 in raw water and direct sources deserve further attention such as additional monitoring. This relates to vinylchloride, trichloroethene, tetrachloroethene, bromodichloromethane, aniline, phenol,1,2-dichloroethane, mevinphos, 2-chlorobenzenamine, 1,4-dioxane, tetraglyme, EDTA, nitrolotriacetic acid and MTBE in the present evaluation. Additional measurements in various water types will (i) indicate whether the concentrations reported here are structurally detected in drinking water (sources), (ii) show the removal efficiency of drinking water treatment processes for individual substances, and (iii) reveal which substances are exclusively found in drinking water and are therefore introduced during the drinking water production process.

It should also be noted that for part of the substances, the potential health impact had not been thoroughly evaluated and pGLVs were based on limited toxicological data. Besides, for some substances, multiple tolerable daily intake levels or drinking water guideline values were reported. An example is trichloroethene, for which the U.S. EPA calculated a lower GLV, based on an additional cancer risk level, than reported by the WHO, which based its GLV on doses causing liver toxicity. In addition, a default allocation of the total exposure to drinking water of 20% was used in the derivation of the pGLVs, while in reality this may deviate per chemical. The drinking water guideline values used in this evaluation may thus alter when new toxicological or exposure information becomes available. They are however considered adequate for the health risk evaluation in the present study, which primarily aimed to prioritize emerging drinking water contaminants for further investigation. For 54% of the selected substances, human health risk assessment could not be performed since relevant toxicity data or drinking water concentrations were lacking. Increased monitoring of drinking water for such CEC is recommended.

For chemicals that lack qualified toxicity data (either included in the present evaluation or other emerging contaminants), TTC levels can be used to estimate their potential human health impact. Here, we calculated generic exposure thresholds based on recent toxicity data available for drinking water relevant substances using the TTC methodology. Cramer classification of these chemicals indicated that they are structurally related to the substances in the TTC databases, and that the chemical structure of the majority of the substances suggests hazardous properties. When the Munro et al. (1996) data set was extended with the drinking water relevant substances, lower TTC values were calculated. The calculated generic exposure thresholds for the emerging drinking water contaminants only are lower than the original TTCs as well, even though mean NO(A)EL values for Cramer class I and III were higher than those derived by Munro et al. (1996). The difference in geometric means for these classes is not explained by a larger number of substances with high NO(A)EL values; the maximum NO(A)EL levels in the present evaluation were lower than those reported by Munro et al. (1996). The lower generic exposure thresholds result from a larger number of substances in the lowest range of NO(A)EL values. These do not include carbamates or organophosphates, for which lower TTC

Table 3
Calculated generic drinking water target levels for recently detected substances in (drinking) water, drinking water equivalent levels, and comparison with (provisional) substance-specific guideline values and available drinking water concentrations.

Chemical group	Number of substances with toxicity data	NO(A)EL values (mg/kg/day) mean (min-max)	Generic exposure threshold (μg/kg bw/day) (*95% C.I.*)	Generic exposure threshold (μg/day)	Original TTC level (μg/day)	Generic drinking water target level (μg/L)	Percentage substances with (p)GLV < target level (n)	Percentage with reported drinking water concentration > target level (n)
Cramer class I	9	204.5 (0.24–1208)	6.22 (*3.80–6.43*)	373.3	1800	37.3	20 (2)	25 (1)
Cramer class III	116	110 (0.01–2916)	0.66 (*0.63–0.66*)	39.7	90	4.0	4.3 (5)	2.6 (3)

C.I. = confidence interval; (p)GLV = (provisional) drinking water guideline value.

values have been reported (Kroes et al., 2004). NO(A)EL values for mevinphos, oxamyl, aldicard sulfoxide and carbaryl are in the middle range and will therefore not affect the calculated Cramer class III exposure threshold value significantly. The larger proportion of low NO(A)EL values might (partly) be caused by the fact that BMDL or LO(A)EL values or therapeutic doses were extrapolated to NO(A)EL values when those were lacking. Other authors have reported lower TTC values for class III as well (Bernauer et al. (2008), Tluczkiewicz et al. (2011). The generic exposure threshold for Cramer class I chemicals is based on a rather small data set. For genotoxic substances, the TTC level of 0.15 μg/day reported by Kroes et al. (2004) was claimed to be protective for the majority of substances, and has even been argued to be overly conservative since the data set on which it has been based is skewed towards high potency carcinogens and contains false positives (EFSA/WHO, 2016). For 10 of the 12 genotoxic substances evaluated in the present study, however, a virtually safe dose was derived below this TTC. This might be due to the fact that these substances predominantly concern carcinogens with high concern for human health for which drinking water guidelines have been derived, and include chemicals for which genotoxicity has not unequivocally been demonstrated.

Based on the exposure thresholds calculated for drinking water-relevant substances, generic drinking water target levels were derived. A target level of 37 μg/L was calculated for Cramer class I substances. The calculated target level for Cramer class III substances (4.0 μg/L) is of the same order of magnitude as reported by Melching-Kollmuß et al. (2010), Dieter (2014) and Laabs et al. (2015) (see Table 1). In those studies, however, a lower drinking water allocation factor of 10% (instead of 20%) was used. Applying this allocation factor in the present evaluation would result in a target level of 2.0 μg/L for class III drinking water contaminants. This target level is still higher than the generic target level of 0.1 μg/L for non-genotoxic substances in drinking water (based on the ToR, which has become obsolete (EFSA/WHO, 2016) since the separate TTC values for genotoxic substances and Cramer classes have been introduced, and on 10% allocation to drinking water) reported by Mons et al. (2013), which may therefore be too conservative with regard to potential health relevance. However, as stated by Mons et al. (2013) target levels > 0.1 μg/L may conflict with the regulatory (non-health-based) guideline value for plant protection products of 0.1 μg/L in the European Drinking Water Directive. In Dutch drinking water legislation, a generic signaling parameter of 1 μg/L for 'other anthropogenic substances' in drinking water and its sources was introduced (Van der Aa et al., 2017). When anthropogenic substances for which no statutory drinking water guideline value has been established are detected above this concentration in the Netherlands, further investigation including toxicological risk assessment is required. This precautionary approach aims to safeguard the chemical quality of sources of drinking water in the presence of many (unknown) chemicals with often limited toxicological information. This signaling parameter of 1 μg/L is approached by the generic drinking water target level calculated for Cramer class III substances in this study, especially when the more conservative drinking water allocation of 10% resulting in a target value of 2.0 μg/L would be used. Hence, this signaling parameter can be regarded as generally sufficiently protective for health effects of drinking water contaminants.

Comparison of the calculated generic drinking water target levels with the substance-specific (p)GLVs demonstrates that TTC approach is conservative by its nature. For over 5% (the cut-off value used in derivation of TTCs) of the Cramer class I substances, however, a substance-specific (p)GLV lower than the calculated generic drinking water target level was derived, probably as a result of the relatively low number of substances in this category. Comparison of the calculated generic target levels with measured drinking water concentrations shows that four substances were detected at higher concentrations, but were present in levels below their substance specific (provisional) drinking water guideline level. This illustrates that generic exposure thresholds are not intended to replace substance-specific toxicological risk assessment; when toxicity data are available, those should be used for health risk assessment. Generic drinking water target levels should also not be applied as stringent target values, but rather as an early warning tool allowing a quick response when contaminants occur in (drinking) water and as reference point for policy making, including priority setting. More detailed assessment of toxicity, exposure and sources, development of analytical methodologies and monitoring programs, and if needed mitigation measures can follow (Van Wezel et al., 2017). Finally, risk assessment based on either chemical-specific health-based guideline values or more generic exposure thresholds and target levels does not include mixture interactions. In individual cases where mixture toxicity is plausible, this can be accounted for by incorporating additional assessment factors in derivation of health-based guideline values.

5. Conclusions

- Out of 686 chemicals present in surface water, groundwater and/or drinking water, 163 were selected as relevant for drinking water.
- For 39 chemicals, (statutory) drinking water guideline values had been reported. For 103 other CECs, (p)GLVs could be derived.
- The majority of the evaluated substances currently detected in drinking water (sources) do not occur in concentrations posing an appreciable risk to human health.
- For 88 of the 163 selected substances, health risk assessment could not be performed since either toxicity data or drinking water concentrations were lacking.
- Generic drinking water target levels of 37 μg/L for Cramer class I substances and 4 μg/L for Cramer class III substances were calculated based on the collected toxicity data. The previously reported generic drinking water target levels based on the original TTC values for non-genotoxic compounds thus seem to be sufficiently protective for human health effects of contaminants of emerging concern in drinking water.
- These target levels are intended for use as an early warning tool and for prioritization of chemicals with unknown toxicity in drinking water and its resources, and do not represent target levels for *all* emerging contaminants.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.05.006.

References

Bernauer, U., Heinemeyer, G., Heinrich-Hirsch, B., Ulbrich, B., Gundert-Remy, U., 2008. Exposure-triggered reproductive toxicity testing under the REACH legislation: a proposal to define significant/relevant exposure. Toxicol. Lett. 176, 68–76.
Bernhardt, E., Rosi, E.J., Gessner, M.O., 2017. Synthetic chemicals as agents of global

change. Front. Ecol. Environ. 15 (2), 84–90.
Bruce, G.M., Pleus, R.C., Snyder, S.A., 2010. Toxicological relevance of pharmaceuticals in drinking water. Environ. Sci. Technol. 44 (14), 5619–5626.
Brüschweiler, B.J., 2010. TTC-based risk assessment of tetrachlorobutadienes and pentachlorobutadienes - the in vitro genotoxic contaminants in ground and drinking water. Regul. Toxicol. Pharmacol. 58, 341–344.
Cheeseman, M.A., Machuga, E.J., Bailey, A.B., 1999. A tiered approach to threshold of regulation. Food Chem. Toxicol. 37, 387–412.
Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Cosmet. Toxicol. 16 (3), 255–276.
De Jongh, C.M., Kooij, P.J.F., de Voogt, P., ter Laak, T.L., 2012. Screening and human health risk assessment of pharmaceuticals and their transformation products in Dutch surface waters and drinking water. Sci. Total Environ. 427-428, 70–77.
Dewhurst, I., Renwick, A.G., 2013. Evaluation of the Threshold of Toxicological Concern (TTC) - challenges and approaches. Regul. Toxicol. Pharmacol. 65, 168–177.
Dieter, H.H., 2014. Health related guide values for drinking-water since 1993 as guidance to assess presence of new analytes in drinking-water. Int. J. Hyg. Environ. Health 217, 117–132.
Dolan, D.G., Naumann, B.D., Sargent, E.V., Maier, A., Dourson, M., 2005. Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. Regul. Toxicol. Pharmacol. 43, 1–9.
EC, 2000a. Commission Regulation (EC) No 1565/2000 of 18 July 2000 Laying Down the Measures Necessary for the Adoption of an Evaluation Programme in Application of Regulation (EC) No 2232/96 of the European Parliament and of the Council.
EC, 2000b. Guidance Document on the Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated Under Directive 91/414/EEC Directorate E – Food Safety: Plant Health, Animal Health and Welfare, International Questions, E1 – Plant Health Sanco/221/2000 – Rev.10-Final.
ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.8: Characterisation of Dose [Concentration]-Response for Human Health. Version 2.1. European Chemicals Agency, Helsinki, Finland.
EFSA, 2012a. Scientific opinion on exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC). EFSA J. 10 (7), 2750.
EFSA, 2012b. Scientific opinion on evaluation of the toxicological relevance of pesticide metabolites for dietary risk assessment. EFSA J. 10 (07), 2799.
EFSA/WHO, 2016. Review of the Threshold of Toxicological Concern (TTC) Approach and Development of New TTC Decision Tree. European Food Safety Authority and World Health Organization. EFSA Supporting Publication 2016: EN-1006.
Etchepare, R., van der Hoek, J.P., 2015. Health risk assessment of organic micropollutants in greywater for potable reuse. Water Res. 72, 186–198.
Feigenbaum, A., Pinalli, R., Giannetto, M., Barlow, S., 2015. Reliability of the TTC approach: learning from inclusion of pesticide active substances in the supporting database. Food Chem. Toxicol. 75, 24–38.
Health Canada, 2016. Science Approach Document. Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances.
Hennes, E.C., 2012. An overview of the values for the threshold of toxicological concern. Toxicol. Lett. 2011, 296–303.
Houtman, C.J., Kroesbergen, J., Lekkerkerker-Teunissen, K., van der Hoek, J.P., 2014. Human health risk assessment of the mixture of pharmaceuticals in Dutch drinking water and its sources based on frequent monitoring data. Sci. Total Environ. 496, 54–62.
Kalkhof, H., Herzler, M., Stahlmann, R., Gundert-Remy, U., 2012. Threshold of toxicological concern values for non-genotoxic effects in industrial chemicals: re-evaluation of the Cramer classification. Arch. Toxicol. 86, 17–25.
Kroes, R., Renwick, A.G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J.G., Würtzen, G., 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem. Toxicol. 42 (1), 65–83.
Laabs, V., Leake, C., Botham, P., Melching-Kollmuß, S., 2015. Regulation of non-relevant metabolites of plant protection products in drinking and groundwater in the EU: current status and way forward. Regul. Toxicol. Pharmacol. 73 (1), 276–286.
Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., Scialli, A.R., Carr, G.J., Felter, S.P., Blackburn, K., Daston, G., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62, 160–182.
Melching-Kollmuß, S., Dekant, W., Kalberlah, F., 2010. Application of the "threshold of toxicological concern" to derive tolerable concentrations of "non-relevant metabolites" formed from plant protection products in ground and drinking water. Regul. Toxicol. Pharmacol. 56, 126–134.
Mons, M.N., Heringa, M.B., van Genderen, J., Puijker, L.M., Brand, W., van Leeuwen, C.J., Stoks, P., van der Hoek, J.P., van der Kooij, D., 2013. Use of the Threshold of Toxicological Concern (TTC) approach for deriving target values for drinking water contaminants. Water Res. 47, 1666–1678.
Munro, I.C., Ford, R.A., Kennepohl, E., Sprenger, J.G., 1996. Correlation of structural class with no-observed-effect levels: a proposal for establishing a threshold of concern. Food Chem. Toxicol. 34, 829–867.
Munro, I.C., Kennepohl, E., Kroes, R., 1999. A procedure for the safety evaluation of flavouring substances. Food Chem. Toxicol. 37, 207–232.
Newcombe, R.G., 1998. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat. Med. 17 (8), 857–872.
Royal Haskoning, D.H.V., 2014. Clean sources for drinking water. In: Anthropogenic chemicals in drinking water abstraction areas in Brabant [Schone bronnen voor drinkwater. Milieuvreemde stoffen in Brabantse waterwingebieden]. Amersfoort, The Netherlands.
Rulis, A., 1986. De minimis and threshold of regulation. In: Felix, C.W. (Ed.), Food Protection Technology. Lewis Publishers, pp. 29–37.
SCCS/SCHER/SCENIHR, 2012. Joint Opinion on Use of the Threshold of Toxicological Concern (TTC) Approach for Human Safety Assessment of Chemical Substances With Focus on Cosmetics and Consumer Products. SCCP/1171/08.
Schriks, M., Heringa, M.B., van der Kooi, M.M., de Voogt, P., van Wezel, A.P., 2010. Toxicological relevance of emerging contaminants for drinking water quality. Water Res. 44 (2), 461–476.
Sjerps, R.M., Vughs, D., van Leerdam, J.A., ter Laak, T.L., van Wezel, A.P., 2016. Data-driven prioritization of chemicals for various water types using suspect screening LC-HRMS. Water Res. 93, 254–264.
Sjerps, R.M.A., ter Laak, T.L., Zwolsman, G.J.J.G., 2017. Projected impact of climate change and chemical emissions on the water quality of the European rivers Rhine and Meuse: a drinking water perspective. Sci. Total Environ. 601-602, 1682–1694.
Tluczkiewicz, I., Buist, H.E., Martin, M.T., Mangelsdorf, I., Escher, S.E., 2011. Improvement of the Cramer classification for oral exposure using the database TTC RepDose - a strategy description. Regul. Toxicol. Pharmacol. 61, 340–350.
URL1 http://monographs.iarc.fr/ENG/Classification, Accessed date: November 2016.
URL2 https://zoek.officielebekendmakingen.nl/stcrt-2016-43.html, Accessed date: November 2016.
Van der Aa, N.G.F.M., van Leerdam, R.C., van de Ven, B.M., Janssen, P.J.C.M., Smit, C.E., Versteegh, J.F.M., 2017. Evaluation Signaling Value Emerging Contaminants Drinking Water Policy [Evaluatie signaleringsparameter nieuwe stoffen drinkwaterbeleid]. RIVM Report 2017-0091. Dutch National Institute for Publiv Health and the Environment, Bilthoven, the Netherlands.
Van Ravenzwaay, B., Jiang, X., Luechtefeld, T., Hartung, T., 2017. The threshold of toxicological concern for prenatal developmental toxicity in rats and rabbits. Regul. Toxicol. Pharmacol. 88, 157–172.
Van Wezel, A.P., Ter Laak, T.L., Fischer, A., Bäuerlein, P.S., Munthe, J., Posthuma, L., 2017. Operationalising solutions-focused risk assessment; mitigation options for chemicals of emerging concern in surface waters. RSC Environ. Water Res. Technol. 3, 403–414.
World Health Organization, 2011. Guidelines for Drinking Water Quality, Fourth Edition. WHO, Genève, Zwitserland.
Yang, C., Barlow, S.M., Muldoon Jacobs, K.L., Vitcheva, V., Boobis, A.R., Felter, S.P., Arvidson, K.B., Keller, D., Cronin, M.T.D., Enoch, S., Worth, A., Hollnagel, H.M., 2017. Thresholds of Toxicological Concern for cosmetics-related substances: new database, thresholds, and enrichment of chemical space. Food Chem. Toxicol. 109 (Pt 1), 170–193.