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# Use of the Threshold of Toxicological Concern (TTC) approach for deriving target values for drinking water contaminants

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ABSTRACT

Ongoing pollution and improving analytical techniques reveal more and more anthropogenic substances in drinking water sources, and incidentally in treated water as well. In fact, complete absence of any trace pollutant in treated drinking water is an illusion as current analytical techniques are capable of detecting very low concentrations. Most of the substances detected lack toxicity data to derive safe levels and have not yet been regulated. Although the concentrations in treated water usually do not have adverse health effects, their presence is still undesired because of customer perception. This leads to the question how sensitive analytical methods need to become for water quality screening, at what levels water suppliers need to take action and how effective treatment methods need to be designed to remove contaminants sufficiently. Therefore, in the Netherlands a clear and consistent approach called 'Drinking Water Quality for the 21st century (Q21)' has been developed within the joint research program of the drinking water companies. Target values for anthropogenic drinking water contaminants were derived by using the recently introduced Threshold of Toxicological Concern (TTC) approach. The target values for individual genotoxic and steroid endocrine chemicals were set at 0.01 μg/L. For all other organic chemicals the target values were set at 0.1 μg/L. The target value for the total sum of genotoxic chemicals, the total sum of steroid hormones and the total sum of all other organic compounds were set at 0.01, 0.01 and 1.0 μg/L, respectively. The Dutch Q21 approach is further supplemented by the standstill-principle and effect-directed testing. The approach is helpful in defining the goals and limits of future treatment process designs and of analytical methods to further improve and ensure the quality of drinking water, without going to unnecessary extents.



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## 1. Introduction

The quality criteria for drinking water in the European Union are described in the Drinking Water Directive 98/83/EC (EC, 1998). Article 4.1 defines the basis for these criteria: 'Water intended for human consumption shall be wholesome and clean if it is free from any micro-organisms and parasites and from any substances which, in numbers or concentrations, constitute a potential danger to human health'. Requirements for a number of chemical and microbiological contaminants and for monitoring frequencies are included in the Directive. Drinking water in the Netherlands complies with the national regulatory requirements for health-based parameters, some of which are more stringent that those in the Directive (Versteegh and Dik, 2007). The high quality is achieved by e.g. applying advanced treatment technologies with multiple barriers and frequent water quality monitoring with advanced analytical techniques. Bottled water consumption in the Netherlands is among the lowest within Europe (FWS, 2009; Geudens, 2012), which may in part be attributed to the high drinking water quality provided by the drinking water companies.

The maintenance of the high quality of drinking water, also in other countries, is challenged by several issues. Firstly, a growing population density, urbanization, climate change with increase of droughts, increasing consumption and intensifying industrial and agricultural activities pose an increasing pressure on the quality of the drinking water sources. Over five million man-made chemicals exist to date, of which approximately 100,000 are included in the European Inventory of Existing Commercial Chemicals Substances (EINECS) list (Van Leeuwen et al., 2007a). Virtually all compounds that are used in society have routes of discharge into the environment and many of these compounds are detected in drinking water sources (e.g. Richardson, 2007; Loos et al., 2009).

Secondly, considerable improvements in analytical chemistry have been achieved in the past decades with about a factor 10 increase in sensitivity achieved each decade. As a result of these improvements in analytical chemistry, many new contaminants as well as known contaminants can be detected (Schriks et al., 2010). To date, such substances are generally designated as 'emerging pollutants', 'emerging substances' or 'emerging contaminants'. There are several definitions of 'emerging contaminants'. In this article the following definition will be used: emerging contaminants are substances that recently have become the focus of attention in drinking water research. Emerging contaminants can be (i) newly introduced compounds, that have never been present before or, (ii) chemicals that have been present for a while but, due to limited analytical capabilities, could not be detected, either because the analytical techniques were not sensitive enough, or because the compound was not included in the analytical methods yet.

For many emerging contaminants no specific drinking water standards exist because of the lack of toxicological information to derive such standards. As an example, since 1983 over 1300 compounds have been detected in river water used for the production of drinking water in The Netherlands. Toxicological information was and still is lacking for about 30–40% of these compounds and for many others only very limited information was available (Van Genderen et al., 2000).

Toxicological information often reveals that the emerging substance is present in drinking water at a concentration below the level that elicits adverse health effects. Consequently, there is no public health problem with the compound, but should the water utilities accept its presence in treated water then? This question has become particularly relevant for pharmaceuticals. Several pharmaceuticals have been detected in drinking water sources, such as analgesics, antibiotics, anti-epileptics, X-ray contrast media and some of them in the range of 10–170 ng/L (Stan et al., 1994; Zuccato et al., 2000; Ternes, 2001; WHO, 2011a). These concentrations are far below levels that might elicit adverse health effects (Christensen, 1998; Schulman et al., 2002; Webb, 2001; Mons et al., 2003; Versteegh et al., 2007). As an illustrative example, Table 1 presents an overview of concentrations of some of the pharmaceuticals detected in treated water in the Netherlands, in comparison with their safe drinking water levels (DWLs) and with their minimum therapeutic doses. The concentrations are all far below the DWLs. Furthermore, lifetime consumption of this drinking water would result in a total accumulated dose ($I_{70}$) of less than one daily dose for therapeutic treatment. Therapeutic health effects are therefore not to be expected, even after chronic exposure, let alone toxic health effects (which usually occur at higher doses than therapeutic effects). Nevertheless, the presence of such pharmaceuticals (Ter Laak et al., 2010; De Jongh et al., 2012) and drugs of abuse (De Voogt et al., 2011) receives a lot of negative media attention and may have a negative effect on consumer confidence in the quality of drinking water.

In 1980, because of a similar situation with pesticides in water, a limit of 0.1 μg/L was introduced for pesticides in the 1980 EC Drinking Water Directive (EC, 1980). This value was based on the principle of 'non-detectability': the philosophy was that pesticides do not belong in drinking water and thus should not be present in it. As the limit of detection at that time was 0.1 μg/L, this became the standard. Should the principle of 'non-detectability' also be applied to other emerging contaminants? The problem is that as detection limits continue to decrease, this principle cannot be maintained. In the 1980's the limit of detection was 0.1 μg/L, currently it is at the ng/L level and in the future it will be even lower, and therefore 'non-detectability' no longer is a feasible concept. With these issues, questions emerge around how to maintain an impeccable drinking water quality:

- How sensitive do analytical methods applied in water analyses need to become? Are they not sufficiently sensitive already?
- How effective do the treatment methods need to become to remove the increasing number of detected contaminants?
- How effective do the treatment methods need to become to reduce concentrations to acceptable safety levels?

To answer these questions, it must be determined what concentration(s) are considered safe and acceptable/tolerable, when (i) toxicological data are lacking, or (ii) toxicological information indicates that the compound has no adverse

**Table 1 – Concentrations of some of the pharmaceuticals detected in treated water in The Netherlands in comparison with safe drinking water levels (DWL) and $I_{70}$ values. Calculations based on Mons et al. (2003) and Versteegh et al. (2007).**

| Compound | Max. Conc. Observed in treated drinking water (ng/L) | DWL[a] (ng/L) | Daily drinking water consumption needed to reach DWL | $I_{70}$ value (mg)[b] | Therapeutic dose (mg/day) | $I_{70}$/therapeutic dose (%) |
|---|---|---|---|---|---|---|
| Acetylsalicylic acid | 122 | $25 \times 10^3$ | 205 L | 6.2 | 20 | 30 |
| Diclofenac | 18 | 7,500[c] | 417 L | 0.9 | 15 | 6.0 |
| Carbamazepine | 90 | $50 \times 10^3$[c] | 556 L | 4.6 | 100 | 5.0 |
| Prozac (fluoxetine) | 10 | 10,000[c] | 1000 L | 0.5 | 20 | 2.5 |
| Bezafibrate | 20 | 35,000[c] | 1750 L | 1.0 | 67 | 1.5 |
| Metoprolol | 26 | 50,000[c] | 1923 L | 1.3 | 100 | 1.3 |
| Fenofibrate | 21 | 50,000[c] | 2381 L | 1.1 | 100 | 1.1 |
| Clofibric acid | 136 | 30,000[c] | 221 L | 6.9 | 1200 | 0.6 |
| Phenazone | 29 | 125,000[c] | 4310 L | 1.5 | 250 | 0.6 |
| Ibuprofen | 28 | $150 \times 10^3$[c] | 5357 L | 1.4 | 300 | 0.5 |
| Paracetamol | 33 | 150,000 | 4545 L | 1.7 | 1200 | 0.15 |
| Lincomycine | 21 | $30 \times 10^3$ | 1429 L | 1.1 | 1200 | 0.1 |
| Sulfamethoxazole | 40 | $75 \times 10^3$ | 1875 L | 2.0 | 2000 | 0.1 |
| Amidotrizoic acid | 83 | $250 \times 10^6$[d] | $3 \times 10^6$ L | 4.2 | 50,000[d] | 0.008 |
| Iopamidol | 68 | $415 \times 10^6$[d] | $6 \times 10^6$ L | 3.5 | 83,000[d] | 0.004 |
| Iopromide | 36 | $250 \times 10^6$[d] | $7 \times 10^6$ L | 1.8 | 50,000[d] | 0.004 |
| Iohexol | 57 | $375 \times 10^6$[d] | $7 \times 10^6$ L | 2.9 | 75,000[d] | 0.004 |

a DWL: safe drinking water level, based on either acceptable daily intake or maximum residue limit.
b $I_{70}$ value: amount ingested after 70 years of consumption of 2 L of drinking water per day, with the maximum concentration of the pharmaceutical observed in drinking water.
c Provisional DWL, based on lowest therapeutic dose and uncertainty factor of 100.
d x-ray contrast medium. The highest dose used, is assumed to have no effect.

health effect, but the compound is not regulated as of yet. Therefore the Dutch water utilities have developed the so-called Q21 approach (Drinking Water Quality for the 21st Century), which is drinking water of impeccable quality (Van Der Kooij et al., 2010). As part of this approach target values (*i.e.* acceptable/tolerable concentrations) have been proposed as an addition to the regulatory standards. This paper describes the derivation of these target values for an impeccable drinking water quality, based on the Threshold of Toxicological Concern (TTC) approach, as well as the other principles of Q21.

## 2. Threshold of Toxicological Concern

For a number of chemicals, toxicological thresholds exist based on toxicological data. These are called Acceptable Daily Intakes (ADIs) or Tolerable Daily Intakes (TDIs) and are the basis for many regulatory standards. Unfortunately, for most chemicals, such as industrial chemicals, toxicological data are not available (Van Leeuwen et al., 2007a; Schaafsma et al., 2009) and alternative approaches are needed for the prioritisation and safety evaluation of these chemicals (Van Leeuwen et al., 2007b). The TTC is a level of human intake or exposure that is considered to be of negligible risk, despite the absence of chemical-specific toxicity data. The TTC approach is a form of risk characterisation in which uncertainties arising from the use of data on other compounds are balanced against the low level of exposure (Munro et al., 2008). The TTC approach has the advantage to offer a safe threshold value in situations where toxicological data are largely or completely absent. The TTC has originally been developed as a 'threshold of regulation' for food contact materials (Rulis et al., 1989; FDA, 1993, 1995) to avoid unnecessary, extensive toxicity testing and safety evaluations. It can be used to assess the likelihood that a particular level of exposure to a chemical would be without toxic effects based on the available toxicity data for a wide range of other chemicals. Following Frawley (1967) and Rulis et al. (1989), Munro (1990) determined from a set of 217 carcinogens that at 0.5 ppb total diet (~1.5 μg/person per day), there would be only a small chance (4%) that a new chemical would give a higher risk for cancer than $1 \times 10^{-6}$ at life-time exposure. Later, Munro et al. (1996) found other, higher thresholds for 613 compounds tested for other toxicity endpoints than carcinogenicity. They divided these compounds into the three structural Cramer classes and found TTCs of 1800, 540 and 90 μg/person per day for Cramer classes I, II and III, respectively. Class I substances are simple chemical structures with efficient modes of metabolism suggesting a low order of oral toxicity, i.e. substances of low concern; class III substances are those that permit no strong initial presumption of safety, or may even suggest significant toxicity or have reactive functional groups, i.e. substances of high concern; substances of intermediate concern are assigned to class II (Cramer et al., 1978).

These TTCs have been adopted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in its evaluation of flavouring substances. Since 1996, a decision tree, incorporating different TTCs related to structural classes, has been used for the safety evaluation of over 1200 flavouring substances (Renwick, 2004). The applicability of the TTC concept for food safety evaluation was further examined by an Expert Group of the European branch of the International Life Sciences Institute (ILSI Europe). These experts concluded that a TTC of 1.5 μg/person per day would provide an adequate margin of safety for both non-cancer and cancer endpoints (Kroes et al., 2000). This conclusion was reconfirmed in a later

paper where also further consideration was given to providing increased safety assurance by the identification of structural alerts for high potency carcinogens and other groups of substances (e.g. neurotoxicants, teratogens, or endocrine disrupting compounds) (Kroes et al., 2004).

It was found that organophosphates form a special group, with a lower TTC than for Cramer class III, i.e. 18 μg/person per day. For compounds with structural alerts or experimental evidence for genotoxicity a TTC of 0.15 μg/person per day was derived. Intake at this threshold gives a 86–97% probability that the cancer risk would be less than $1 \times 10^{-6}$ (Kroes et al., 2004). Aflatoxin-like compounds, azoxy compounds and N-nitroso compounds were excluded from the TTC approach as they are high potency carcinogens, showing a high probability (45–100%) for a risk higher than $1 \times 10^{-6}$ even at the TTC for genotoxins at 0.15 μg/person per day (Kroes et al., 2004). Risk assessment of substances included in such groups therefore requires compound-specific toxicity data. In the same paper of Kroes et al. (2004), a decision tree is described using a tiered approach that results in different TTC values for the different defined groups of compounds (see Table 2).

The initial step of applying the TTC approach is the exclusion of compounds for which no TTC could be derived (Kroes et al., 2004; EFSA, 2012). According to EFSA (2012), the TTC approach should not be used for the following (categories of) substances:

- High potency carcinogens (i.e. aflatoxin-like, azoxy- or N-nitroso-compounds, benzidines, hydrazines).
- 1Inorganic substances
- Metals and organometallics
- Proteins
- Steroids
- Substances that are known or predicted to bioaccumulate
- Nanomaterials
- Radioactive substances
- Mixtures of substances containing unknown chemical structures

**Table 2 – TTC levels for the different defined groups of compounds.**

| Compound group | TTC (μg/person per day) |
|---|---|
| • Excluded chemicals: (groups of) chemicals such as high potency carcinogens, e.g. aflatoxin-like, azoxy- or N-nitroso compounds, benzidines, hydrazines), inorganic substances, metals and organometallics, proteins, substances that are known or predicted to bioaccumulate, nanomaterials, radioactive substances and mixtures of substances containing unknown chemical structures | None |
| • Compounds with structural alert or experimental evidence for genotoxicity | 0.15 |
| • Non-genotoxic compounds, except for those given below | 1.5 |
| • Organophosphates | 18 |
| • Compounds in Cramer class III | 90 |
| • Compounds in Cramer class II | 540 |
| • Compounds in Cramer class I | 1800 |

This first step of exclusion is followed by the identification and evaluation of possible genotoxic and/or high potency carcinogens through structural alerts. Non-genotoxic substances are then classified as organophosphate and carbamate substances with anti-cholinesterase activity or as Cramer classes I, II and III. This categorization or classification of the chemicals leading to the appropriate TTC, can be achieved with e.g. the OECD QSAR application toolbox (URL1). According to EFSA (2012) the original FDA Threshold of Regulation value of 1.5 μg/person per day is of historical importance, it has little practical application in the overall TTC approach for food and feed safety. However, such "default" TTC is of practical relevance in setting water quality target values in case of limited toxicological information, because the drinking water target values derived by higher TTC values would not match with current standards for e.g. pesticides in drinking water. Therefore, the original FDA Threshold of Regulation value of 1.5 μg/person per day is maintained.

While the TTC concept has an obvious advantage in prioritisation of chemicals and safety evaluation of chemicals by reducing animal testing and testing costs, some downsides and concerns around this concept have been reported as well (Kroes et al., 2004; EFSA, 2012; Dewhurst and Renwick, 2013). These downsides include:

1. The TTC does not consider mixture effects, while reports exist on how chemicals at individual ineffective concentrations can cause effects in a mixture (EC, 2009). This issue is dealt with below, in Section 3.2.
2. The determination of the TTC relies on sufficient data, and on data quality. However, the databases used for the derivation of the TTC contain quite "old" data, from traditional tests using relatively high doses, while new data, from newer tests and new technologies such as genomics and with more focus on low-dose effects and toxicological mode of action, are currently generated.
3. The TTC is a probabilistic approach and therefore not protective of all chemicals (the protective level was set at 95%, see above).
4. The range of chemicals in the supporting databases and the 'applicability domain' is limited. Furthermore, concerns have been expressed about the tools used to identify structural alerts to allocate chemicals into the different classes.
5. There are concerns about the suitability of the Cramer decision tree for dividing chemicals into different classes of toxic potential and whether certain chemicals should be excluded *a priori* from the TTC approach.
6. Use of the TTC requires accurate exposure data, which are very often not available (for drinking water this is probably not a big issue, as measured concentrations are available for many chemicals).
7. It has been argued that if the TTC is used to waive further testing, no further data are produced to keep verifying whether the TTC is indeed a proper threshold for waiving

Concerning the second issue, a recent review on low-dose effects does find effects at doses below those traditionally used in toxicity tests (Vandenberg et al., 2012). There are also examples of effects observed at doses far below those related to the TTCs of Cramer class III (e.g. Macon et al., 2011; Andrade et al., 2006). However, we have not yet seen reports of effects observed at doses below those related to the default TTC of 1.5 μg/d (considering the usual safety factors). This value therefore appears to be sufficiently protective, which is another reason to keep including this value. This issue remains a subject of attention, however, and it is desirable that the protective value of the TTCs is regularly reviewed with the latest knowledge and data.

## 3. Deriving drinking water target values with the TTC approach

### 3.1. *Single chemicals*

The TTC concept provides a useful basis for deriving threshold levels for contaminants in impeccable drinking water. Kroes et al. (2004) already indicated that "the TTC principle may be more broadly applicable than simply to chemicals in food. It has potential value in the assessment of other exposure scenarios". Dutch drinking water companies aim at reducing the concentrations of contaminants to a level which (i) cannot have any adverse health effect, (ii) demonstrates that control measures are highly effective for all contaminants, and (iii) support consumer confidence. For defining water quality Q21 it is proposed to use the two lower TTC values, *i.e.* 0.15 μg/person per day for compounds with an indication for genotoxicity and 1.5 μg/person per day for non-genotoxic compounds. At these levels, health effects are prevented for nearly all organic contaminants (the exceptions are the groups excluded for the TTC; see Table 2). Higher TTC values, up to 1800 μg/person per day, as have been mentioned by Munro et al. (1996) and Kroes et al. (2004), are considered inappropriate for treated drinking water, even if it is known that they do not cause adverse health effects. This is an ethical argument following from the philosophy that contaminants do not belong in impeccable drinking water. This philosophy is in line with the legislation for pesticides (0.1 μg/L) in the European Drinking Water Directive (EC, 1998).

The TTC values, as given in Table 2, are total exposures per person per day. To derive drinking water target values, these therefore need to be translated to drinking water concentrations. As the TTC values were determined for oral exposure, too, no correction for the type of exposure route is necessary. However, it must be taken into account that ingestion through drinking water is only part of the possible daily exposure. Standards or guideline values for drinking water based on a Tolerable Daily Intake (TDI) or Acceptable Daily Intake (ADI) take into account exposure from all sources by allocating a percentage of the ADI to drinking water. Wherever possible, data concerning the proportion of ADI normally ingested in drinking water are used for establishing the target values. When such information is not available, an arbitrary and conservative default value of 10% is used. As default exposure variable, the standard World Health Organization drinking-water consumption rate of 2 L/day for adults (60 kg) is used (WHO, 2011b). Using the TTC value of 0.15 μg/person per day for genotoxic substances and a TTC of 1.5 μg/person per day for non-genotoxic compounds, the following target values (as rounded figures) can be derived:

(a) Target value for genotoxic chemicals: $\frac{0.15\ \mu g/\text{person per day} \times 10\% \approx 0.01\ \mu g/L}{2\ L}$

(b) Target value for other chemicals: $\frac{1.5\ \mu g/\text{person per day} \times 10\% \approx 0.1\ \mu g/L}{2\ L}$

The proposed target values are summarized in Table 4. As steroid hormone compounds are abundantly found in surface water and are thus of concern for drinking water quality, it was deemed necessary to include these compounds in the list of proposed target values, despite the opinion of EFSA (2012) to exclude them in the TTC approach. For the natural estrogen 17β-estradiol, an ADI of 50 ng/kg bw per day has been reported (IPCS, 2000). With the drinking water allocation factor and daily consumption given above, this could be translated to a drinking water limit value of 150 ng/L. This value is probably much too high because of the low oral absorption and bioavailability of this specific compound as compared to other steroid compounds (especially those synthesized for pharmaceutical purposes), which are often much better absorbed and bioavailable. Of 17β-estradiol only 2–10% is absorbed from the gastrointestinal tract into the bloodstream, where 95–98% is unavailable because it is bound to serum proteins (O'Connell, 1995). Assuming a realistic worst case where other steroid hormones are better absorbed (i.e. 100%) and similarly unavailable in the blood (i.e. 95% unavailable, due to albumin binding mostly; Heringa et al., 2004), it was deemed best to apply the same target value for steroid hormones as that for genotoxic chemicals: 10 ng/L. This proposed target value of 0.01 μg/L is supported by the work of Mennes (2004), who proposed a concentration of 7 ng EEQ/L (Estradiol Equivalents) as determined by the ER-CALUX assay as a trigger value above which further studies are warranted. We are currently performing an in depth review on this specific topic, based on earlier observations of Van der Linden et al. (2008).

Detected contaminants can be screened for genotoxicity or a steroid hormone structure by using QSARs. These models screen a given chemical structure for the presence of e.g. a steroid structure, or the presence of functional groups that are known to be related to, e.g. genotoxicity of a compound (URL1).

### 3.2. *Mixtures*

In drinking water, many different compounds can be present individually at concentrations below the target values, but as a mixture, the sum of all compounds together might still cause undesirable health effects (EC, 2009). Therefore, it is justified to set a target value for the sum of all contaminants, to avoid the presence of a wide variety of compounds at levels just below their individual target value.

The risk assessment of mixtures is a complex matter, has a long history and is still under debate. The review of Kortenkamp, Backhaus and Faust (EC, 2009) shows how both concentration addition (CA) and independent action (IA) have

**Table 3 – Mode of action of the fifteen contaminants with highest maximally detected levels in drinking water from Schriks et al. (2010).**

| Compound | Maximally detected level in drinking water (μg/L) | Indication of mode of action (MoA) | Source |
|---|---|---|---|
| EDTA (ethylenediamine tetra acetic acid) | 13.6 | Zinc deficiency through complexation[a] | WHO, 2011b |
| DTPA (diethylene triamine penta acid) | 9 | Fetal deformation (developmental toxicity) | ECB, 2000 |
| Metoprolol | 2.1 | Beta-blocker[b] | Versteegh et al., 2007 |
| BCIPE (bis(chloroisopropyl)ether) | 1.9 | Decreased haemoglobin | US EPA, 1989 |
| Trichloroethene | 1.75 | Heart malformations (developmental toxicity) | WHO, 2011b |
| MTBE (methyl tert-butyl ether) | 1.25 | Liver, kidney | Swartjes et al., 2004 |
| AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) | 1.1 | Renal tubule dialation in offspring (developmental toxicity)[c] | WHO, 2011b |
| Benzene | 0.96 | Non-genotoxic carcinogenicity | WHO, 2011b |
| PFOA (perfluoroctane sulfonate) | 0.52 | Liver (possibly through PPAR receptor) | EFSA, 2008 |
| 1,4-dioxane | 0.5 | Non-genotoxic carcinogenicity | US EPA, 1988 |
| Glyphosate | 0.46 | Renal tubule dialation in offspring (developmental toxicity)[c] | WHO, 2011b |
| Bentazone | 0.28 | Haematological effects | WHO, 2011b |
| Amidotrizoic acid | 0.25 | None known | Versteegh et al., 2007 |
| Diglyme (diethylene glycol dimethyl ether) | 0.15 | Developmental toxicity | WHO, 2002 |
| Clofibric acid | 0.14 | Effects on serum cholesterol and triglycerides | Versteegh et al., 2007 |

a The MoA is not well characterized, this is the assumed MoA.
b Toxic effects have not been well reported, the provisional guideline value was based on the lowest therapeutic dose; the therapeutic MoA is as a beta-blocker.
c AMPA is the metabolite of glyphosate, these have the same critical mode of action.

been applied successfully to predict mixture toxicities (EC, 2009). CA applies when chemicals have the same mode of toxicological action; their concentrations (corrected for the relative potency of the compounds) can then be added up to a virtual total concentration, leading to a predicted total effect. IA applies when chemicals act independently of each other, through different toxicological pathway. In this case, not the concentrations, but the final effect levels of the mixture components can be added up. At low levels of individual chemicals, beneath toxicological thresholds, CA can lead to toxic effects of the total mixture, while with IA, the mixture does not lead to toxic effects. The report gives some examples, however, that even mixtures of chemicals with different modes of action each, can lead to a higher toxic effect than the individual chemicals cause, falsifying the assumption of IA (EC, 2009, section 6.6). From a precautionary view, CA therefore seems to be the safer assumption and estimation method, also because its predictions have shown to be on the more conservative (i.e. safer) side.

**Table 4 – Proposed target values for organic contaminants in drinking water.**

| Compound group | Target value (μg/L) |
|---|---|
| Single genotoxic organic chemicals | 0.01 |
| Single (synthetic) steroid hormones | 0.01 |
| All other single organic chemicals | 0.1 |
| Total sum of genotoxic compounds | 0.01 |
| Total sum of (synthetic) steroid hormones | 0.01 |
| Total sum of all other organic chemicals | 1.0 |

As a leading example in regulation, the US EPA has produced guidance on the cumulative risk assessment of pesticides, where the different pesticides are divided into groups sharing a common toxic effect and the mixture effect is calculated by CA (US EPA, 2002). This approach is not feasible for these target values, as knowledge on the type of toxic effects of all present compounds in the water is then necessary, while this is not available. The IPCS (WHO) has also published a framework for the risk assessment of mixtures of chemicals, also based on CA, but with a tiered approach for the specific data needed to determine whether a risk can be expected (Meek et al., 2011). The publication gives an example of how, in a first tier, maximum found drinking water contaminant levels can be divided by the appropriate TTC, to derive a hazard index for each compound, which can be summed to obtain an estimation of the worst case toxicity of the mixture. If this worst case calculation already shows no risk, no further efforts are necessary. This approach is very useful in assessing current situations in an efficient manner.

This IPCS framework could serve as a basis to derive maximum levels for the total of chemical pollution in drinking water. This would imply that the total of all concentrations of the individual compounds should not exceed the target value derived for the individual chemicals: 0.1 μg/L. However, this target value would be very difficult to reach and thus would imply high investment costs for drinking water utilities, while this is probably not necessary. This approach is too conservative for this purpose, as it assumes that each chemical has the same high toxic potency. Furthermore, it assumes CA, i.e. that the chemicals act through virtually the same toxic pathway. This is not to be expected. As a crude example, Table 3

lists the modes of action of the fifteen compounds with highest maximally detected levels in drinking water from Schriks et al. (2010). Among these ten compounds, roughly seven different modes of action can be distinguished, when liver effects are bundled, as well as all types of developmental toxicity and the different haematological effects.

The report of Kortenkamp, Backhaus and Faust states that the compounds in a heterogenous mixture (such as drinking water) will act in an intermediate fashion between concentration addition (CA) and independent action (IA) (EC, 2009, p. 22). With these considerations, together with the conservative approach for the individual target values already, it does not seem justified to set a mixture target value at the same level as the individual target value (0.1 μg/L).

Instead, a pragmatic approach is taken, intermediate between CA and IA, roughly estimating that the most abundant drinking water contaminants have around ten different modes of action (Table 3). Thus, the target value of the total mixture is set at ten times the individual target value, i.e. at 1 μg/L. As a practical and regulatory advantage, this value matches well with the limit value of 0.5 μg/L for the sum of pesticides (EC, 1998), allowing the regulatory 0.5 μg/L of total pesticides to be present in the drinking water (or less of course), besides another 0.5 μg/L for other types of compounds. We acknowledge that this is a pragmatic approach. It is therefore desirable that further research is performed on the mixture toxicity of drinking water contaminants, including their modes of action and whether CA applies or not.

For the genotoxic compounds and steroid hormones, it is clear they have a similar mode of action, so CA must be applied. Thus, the target value for the total of genotoxic compounds must be set at the level of the individual compounds, i.e. 10 ng/L, and idem ditto for the total of steroid hormones. The report of Kortenkamp, Backhaus and Faust gives examples where even synergism (i.e. the mixture gives higher effects than expected based on CA) is observed in carcinogenicity studies with mixtures (EC, 2009, section 4.1). It may therefore be argued that the target values for the individual and total of genotoxic compounds should actually be lower than the TTC of 10 ng/L. However, it must be remembered that the TTC is already very conservative, and recent analyses have found that with CA, synergistic effects are underestimated only by one order of magnitude. In the case of steroid hormones, it may be argued that compounds with a different target receptor (e.g. an estrogen and an androgen) act differently and have different effects, and should therefore not be grouped together for the same mixture target value. This is dismissed by the fact that the steroidogenesis pathways and the steroid action pathways are highly interconnected, therefore IA does not seem appropriate in this case.

Table 4 summarizes the proposed target values for drinking water for single organic chemicals and their mixtures.

## 4. Discussion

### 4.1. *Comparison of target values to current standards*

Table 5 shows a comparison of the current limit values for organic contaminants as valid in the Netherlands (similar to the EU Directive) with the proposed target values. For an international and purely health-based perspective, also the available guideline values of the WHO are given, which differ from the Dutch limit values for most compounds. This difference is due to slight differences in the risk assessment methods and to the consideration of what is realistically achievable with current technologies in the Dutch limit values. We have deliberately used a conservative allocation factor of 10% that reflect the likely contribution of water to total daily intake for various chemicals. Recently the WHO (2011b) has increased the percentage of total daily intake through drinking-water for adults for threshold chemicals to 20%, to reflect a reasonable level of exposure based on broad experience, while still being protective. This new WHO value reflects a change from the previous allocation of 10%. It is clear that the proposed target values are equal to or lower than the current limit and guideline values. This indicates that the proposed target values are indeed sufficiently protective for human health risk.

The target value of 0.1 μg/L for single non-genotoxic and non-steroid compounds also corresponds well with the non-health-based current EU limit value of 0.1 μg/L for pesticides (EC, 1998). This strengthens the choice of not accepting higher TTC levels from an ethical point of view: higher levels would not be accepted by regulators for the pesticides at least, even if they do not cause adverse health effects either. The target value of 1.0 μg/L for the sum of non-genotoxic and non-steroid compounds corresponds well with the limit values for the sum of pesticides (0.5 μg/L) and the sum of PCBs (0.5 μg/L) together, but is a bit more stringent than the sum of all limit values together (e.g. also the sum of PAHs). Compliance to the target values will therefore lead to compliance to the regulated limit values without requiring large deviations from these limit values. We realize that for the regulatory implementation of the targets for the sum parameters (as in the case of PAHs and PCBs) further concrete recommendations on the analytical methods and analytical windows still needs to be developed.

The Danube–Meuse–Rhine memorandum of 2008 (IAWR, 2008) gives target values for chemicals in these rivers, with the aim of increasing the quality of these drinking water sources in such a manner that only near-natural (very basic) treatment techniques are sufficient for the production of drinking water. The target value for contaminants with specific biological activity (e.g. pharmaceuticals, hormones, and pesticides) should not exceed a level of 0.1 μg/L. This value corresponds well with the target value proposed in this paper, except for the steroid hormones and genotoxic compounds. It would be worthwhile to collect and where necessary create more data on acceptable levels of steroid hormones in drinking water, to make a choice from the two different target values with a more solid basis than available currently. This is not necessary for genotoxic compounds, as these have been studied for the derivation of the special TTC by Kroes et al. (2004) already. Compounds without known biological activity have been given a target value of 1 μg/L in the memorandum, while complexing agents may be present up to 5 μg/L. These values are higher than the target value proposed in this paper.

**Table 5 – Comparison of current limit values in the Netherlands and the guideline values of the WHO, and the proposed target values.**

| Compound[a] | Limit value (μg/L) | Source limit value[b] | Proposed target value (μg/L) |
|---|---|---|---|
| Acrylamide (G) | 0.10 | Dutch DWD, 2011 | 0.01 |
| | 0.50 | WHO, 2011b | |
| Benzene (G) | 1.0 | Dutch DWD, 2011 | 0.01 |
| | 10 | WHO, 2011b | |
| Benzo[a]pyrene (G) | 0.010 | Dutch DWD, 2011 | 0.01 |
| | 0.7 | WHO, 2011b | |
| 1,2-dichloroethane (G) | 3.0 | Dutch DWD, 2011 | 0.01 |
| | 30 | WHO, 2011b | |
| Epichlorohydrine (G) | 0.10 | Dutch DWD, 2011 | 0.01 |
| | 0.40 | WHO, 2011b | |
| PAHs (sum) (G) | 0.10 | Dutch DWD, 2011 | 0.05[d] |
| PCBs (individual) | 0.10 | Dutch DWD, 2011 | 0.1 |
| PCBs (sum) | 0.50 | Dutch DWD, 2011 | 1.0[e] |
| Pesticides (individual) | 0.10 | Dutch DWD, 2011 | 0.1 |
| Pesticides (sum) | 0.50 | Dutch DWD, 2011 | 1.0[e] |
| Tetra- and trichloroethene | 10 | Dutch DWD, 2011 | 0.2[c] |
| Tetrachloroethene | 40 | WHO, 2011b | 0.1 |
| Trichloroethene | 20 | WHO, 2011b | 0.1 |
| Trihalomethanes (sum) | 25 | Dutch DWD, 2011 | 1.0[e] |
| Vinylchloride (G) | 0.50 | Dutch DWD, 2011 | 0.01 |
| | 0.30 | WHO, 2011b | |

a G = genotoxic chemical.
b Dutch DWD = Dutch drinking water directive; WHO, 2011b.
c Calculated as sum of guideline/target values for both individual compounds.
d With consideration that this maximum is meant for the sum of all genotoxic contaminants, not only this group of genotoxic chemicals.
e With consideration that this maximum is meant for the sum of all contaminants, not only this group of chemicals.

### 4.2. *Comparison to approaches applied in Germany and in the USA*

In Germany and the USA, approaches have also been defined for emerging contaminants in drinking water. The Drinking Water Regulation in Germany is based on the European Drinking Water Directive (EC, 1998). Next to tables with standards for several parameters it states that drinking water quality should be such that it is acceptable for human health for lifelong consumption (TWVO, 2001). The German Federal Environmental Agency has developed recommendations for situations where a toxicological evaluation is not, or only partially, possible. A pragmatic health-based protection value (HPV) of 0.1 μg/L has been defined as a precautionary value, which should allow lifetime consumption (*i.e.* 70 years) of drinking water (UBA, 2003). The value of 0.1 μg/L applies to both non-genotoxic compounds and the majority of genotoxic compounds. For highly genotoxic compounds it is indicated that this value cannot be used for lifetime exposure, but only for a short (70 years/(measured concentration/HPV)) duration (UBA, 2003 And a value of 0.01 μg/L should be used for longer durations (personal communication Tamara Grummt, UBA). Depending on the amount of toxicological information available, the German Federal Agency indicates that higher levels can be used as HPV. Table 6 shows that for non-genotoxic compounds in drinking water, for which toxicological data exist, HPVs can be up to, or even over 3 μg/L, depending on the quality of the available information. The HPVs are recommendations for situations where a toxicological evaluation is not or only partially possible and are not mandatory.

The default HPV and the HPV for highly genotoxic substances correspond well with the target value proposed in this paper, except for the target value of steroid hormones. The fact that higher HPVs can be applied for chemicals for which there are toxicological data showing sufficient safety, is explained by the fact that the HPVs only consider the prevention of adverse health effects (as their name indicates), and not the principle that anthropogenic contaminants do not belong in drinking water. Another difference of the proposed

**Table 6 – Maximum values for lifelong exposure to unregulated contaminants in drinking water in Germany (UBA, 2003).**

| HPV (μg/L ) | Explanation |
|---|---|
| 0.1 | No toxicological data available. |
| ≤0.3 | Only genotoxicity data available, indicating the substance to be non-genotoxic. No other toxicological data available. |
| ≤1 | Substance proven non-genotoxic (see above). Data on neurotoxicity and germ cell damaging potential available, not indicating a value <0.3 μg/L. |
| ≤3 | Substance neither genotoxic nor germ cell damaging nor neurotoxic. *In vivo* data on subchronic oral toxicity available, not indicating a value lower <1 μg/L. |
| >3 | At least one chronic oral study is available enabling (almost) complete toxicological information and not indicating a value <3 μg/L. |

target values, compared to the German approach, is that, in addition to target values for individual compounds, the use of sum values (1.0 μg/L and 0.05 μg/L for non-genotoxic and genotoxic compounds, respectively) is included in the Q21 concept. These sum values are intended to prevent possible effects from mixtures of contaminants in drinking water. Furthermore, the presence of a range of contaminants at concentrations just below their individual target value is undesirable, because it demonstrates that a variety of contaminants can pass drinking water treatment.

Drinking water standards in the USA are defined as Maximum Contaminant Levels under the Safe Drinking Water Act (SDWA; (US EPA, 1996). The US Environmental Protection Agency periodically releases a Candidate Contaminant List (CCL) with 'new' contaminants that are known or anticipated to occur in drinking water sources and might require regulation. This CCL is closely related to the Unregulated Contaminant Monitoring Rule (UCMR) that requires drinking water utilities to monitor several unregulated contaminants for a certain period. These data are evaluated together with health effects data to determine whether any new compounds should be regulated. The first CCL was prepared in 1998, the third in 2009 (US EPA, 2009).

When determining whether or not to regulate a contaminant three aspects are considered: (i) projected adverse health effects, (ii) the extent of occurrence in drinking water, and (iii) whether regulation of the contaminant would present a 'meaningful opportunity' for reducing risks to health (URL2). Until now this process has not resulted in the regulation of additional parameters in the SDWA.

Thus, in the USA, no general limit or target value is used for the unregulated contaminants, but instead for each contaminant a specific health-based limit value is derived. The Dutch Q21 approach differs from the US approach with the Contaminant Candidate List where information on adverse health effects is essential in deciding whether or not to regulate the specific compound. The CCL process is a substance-specific approach which needs to be conducted for each individual contaminant, whereas the target values derived in this paper can be applied to all substances. In addition, the US approach does not provide guidance for situations where compounds are detected in drinking water in concentrations below toxicological standards.

### 4.3. *Application of the target values*

Drinking water companies in the Netherlands comply with the regulatory standards and Water Safety Plans (WHO, 2011b) are presently introduced to further ensure such compliance. The Q21 target values based on the TTC approach for genotoxic, steroid, and other organic chemicals provide guidance in those situations where contaminants are detected in drinking water, but toxicological data are lacking (Van Der Kooij et al., 2010). When the detected level is below the target values, no action is necessary. If the detected level of a contaminant is above the target values, it is desirable to reduce the concentration below the target levels in the future. The urgency of reduction measures then depends on whether there is a health risk, for which additional toxicological research is then justifiable. In case this additional research proves that the contaminant is present in drinking water in concentrations below those that elicit adverse health effects, there is less urgency to reduce the concentration, but compliance to the target values is still desirable. This also applies to the contaminants for which toxicological data are already present, which indicate no health risk.

The target values are not intended for use as stringent standards but serve as a reference point on which policies for the future can be based. The described approach intends to identify priorities and to facilitate the achievement of drinking water with a very high quality (Q21). For example, when a drinking water utility evaluates its current water treatment performance and wants to make plans for improvement, the target values can serve as the reference point: do the current levels in the final drinking water comply with the target values and if no, which technology should we apply to achieve compliance? Alternatively, the figures of non-compliance can be used to further reduce the emission of a contaminant. Depending on the current compliance, the urgency regarding health risks, and other socio-economic and political considerations may then determine the route to finally achieve compliance to these target values. As a side effect, applying the target values to the known emerging contaminants will result in a further pressure to reduce other potentially hazardous contaminants passing the applied treatment barriers.

The research efforts can also be framed with these target values. Analytical methods do not have to become more sensitive than around 5 ng/L (half of the lowest target value), to be able to reliably analyse compliance to the individual target values and to detect trends towards non-compliance. Concerning compliance to the mixture target values, such sensitivity also enables the analysis of compliance for 200 non-genotoxic and non-steroid contaminants (as $200 \times 5$ ng/L $= 1$ μg/L). For genotoxic and steroid compounds, more sensitive methods will be necessary to analyse compliance to the 10 ng/L mixture target values of these type of compounds. It would be useful if an analytical method could be designed to determine the total load of organic contaminants. Effect-directed toxicity tests for e.g. genotoxicity and endocrine activity are a step in this direction, as the total toxic activity (not concentration!) of the mixture in water is determined. These tests are further discussed in 4.4.

Research efforts concerning more efficient treatment technologies or combinations of different technologies may also be directed towards achieving removal efficiencies sufficient to ensure compliance to the target values. Higher efficiencies are not necessary, saving further research resources. The necessary efficiencies are of course dependent on the local levels of contaminants in the raw water. For some compounds, the target values can prove impossible to achieve with current technologies. In that case, motivated exceptions can be made, applying specific limit values that are as low as reasonably achievable, next to the health-based regulatory values.

The target values apply to organic contaminants that have not been formally regulated in drinking water legislation as well as substances that are already included in drinking water quality regulations. Drinking water standards are often solely health-based, while the proposed target values are also

based on the ethical aspect that contaminants do not belong in our drinking water. It is therefore justified that the proposed target values are somewhat more stringent than health-based standards. This can be seen as a precautionary approach and compounds can be evaluated on a case by case basis once adequate toxicological information has become available.

### 4.4. *Additional Q21 principles*

Apart from the TTC-based target values, there are two complementary pillars embedded in the Q21 strategy: (1) an effect-based approach for the assessment of water quality and (2). the standstill principle (the quality of water should at least remain at its present level) and not decrease. Effect-directed tests using cell lines or micro-organisms are able to detect the overall biological effect of all substances present, when isolated from water. These tests can provide additional data when information is needed on possible health effects without knowing what substances or concentrations are present, or can therefore be used as a screening tool to waive further chemical analytical investigations with respect to the specific endpoint studied. Additionally, these tests are useful in determining the total mixture toxicity since the total biological activity is measured. Examples of commonly used tests include the Ames assay for detecting genotoxicity and the CALUX bioassays for detecting specific endocrine activity (Ames et al., 1973; Sonneveld et al., 2005, 2006, 2011). With these assays effects have been observed in river water and ground water (which may be used for drinking water production), but not in treated, non-chlorinated, drinking water (e.g. Kool et al., 1982; Veenendaal and Van Genderen, 1999; Helma et al., 1998; Reifferscheid and Grummt, 2000; Abrahamse et al., 2007; Alink et al., 2007; Van der Linden et al., 2008; Heringa et al., 2011). Further research is necessary to indentify (i) the (battery of) tests required for water quality monitoring and (ii) the target values for the response of these assays. In the meantime, the stand-still principle is applied for the effect-directed tests, too: effect levels should not increase when applying the same measurement methodology (as changes in the analysis method can change the detection levels).

## 5. Conclusions

- Based on the TTC approach, we propose target values for organic contaminants in drinking water as given in Table 4.
- These target values correspond well with most current standards, but they are sometimes more conservative.
- The target values can be used in quality evaluations, future plans and policy support of drinking water utilities and serve as a framework for research efforts.
- Application of these target values can contribute to lasting consumers' confidence. It will not only show that drinking water is safe (the water fulfils drinking water standards), but also illustrate that quality aims and efforts of these drinking water companies go beyond this point to produce impeccable drinking water.

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