Threshold of Toxicological Concern approach for deriving target values for drinking water contaminants

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Shareholders of **KWR**: Drinking water utilities

Drinking water production (in million m³)

- 44
- 32
- 345
- 88
- 86
- 76
- 176
- 178
- 71
- 41
ITS and drinking water

1. Short intro Risk Assessment
2. Deriving (no) effect levels
3. The concept of TTC
4. Proposed TTC values
5. Conclusions
Exposure assessment is crucial
Exposure pathways of man

Environment
- air
- water
- food
- soil

Consumer products
- oral
- inhalation
- dermal

Occupational environment
(Emerging) pollutants in the (aqueous) environment

Production, use and disposal can lead to emission of anthropogenic compounds in the environment, e.g.

- Industrial chemicals
- Plant protection products
- Biocides
- Veterinary drugs
- Human drugs
- Feed & Food additives
- Cosmetics
- Intermediates/degradation products/etc.
Regulatory decisions

- Scientific aspects
- Risk assessment
- Technical feasibility
- Legislative/political factors
- Social/economic factors
- Ethical/cultural values
Background of Risk Management of Drinking Water

How clean is clean?
How clean is clean enough?

Fitness for use

Available Technology
Cleanup Goals
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Water safety (goals)
Defining thresholds fit (safe) for purpose

Microbial and chemical quality standards to meet demands for purpose

- drinking water
- industrial water,
- agricultural water
- water in the environment

This presentation: Chemical quality of drinking water
Deriving No effect levels

Step 1
Compare occurrence concentrations to existing legal or advisory thresholds or..

Step 2
Find surrogate thresholds in other fields of science, e.g. Pharmacy, or..

Step 3
Use generic (protective) thresholds based on statistical approaches
Toxicological evaluation
Derivation of Provisional drinking water guidelines

Chronic effects of a compound in lab animals (NO(A)EL) or BMD

Uncertainty factors

Extrapolate to a human Acceptable Daily Intake (ADI) / Tolerable Daily Intake (TDI) / Reference Dose (RfD)

70 kg bw, 2 L consumption, 10-20% allocation to DW

Calculate a (provisional) drinking water guideline value (pGLV) *

* pGLV = TDI (µg/kg/day) x average weight adult (70 kg) / 2 L water per day x 10% allocation factor
Toxicological evaluation of emerging contaminants
Application of provisional drinking water guideline values

1. List of emerging substances relevant for the watercycle
   - NO
   - YES
     - log Kow > 3
       - Statutory GLV available?
         - YES
           - WHO, U.S. EPA, other
             - Cat A compound
         - NO
           - Less relevant – no evaluation
 2. Log Kow > 3
   - YES
   - NO
     - Statutory GLV available?
       - YES
         - Established ADI, RfD, TDI etc. Available?
           - YES
             - Calculate Provisional GLV
               - Cat B compound
           - NO
             - Calculate TDI
               - Calculate Provisional GLV
                 - Cat C compound
         - NO
           - Established LO/NO(A)EL available?
             - YES
               - Calculate TDI
                 - Calculate Provisional GLV
                   - Cat D compound
             - NO
               - Other “miscellaneous” toxicological information available?
                 - YES
                   - Calculate TDI
                     - Calculate Provisional GLV
                       - Cat D compound
                 - NO
                   - Insufficient data – no evaluation
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TTC definition

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 characterization in which uncertainties arising from the use of data on other compounds are balanced against the Low Level of exposure.

The TTC approach has the advantage to offer a safe threshold value in situations where toxicological data are largely or completely absent.
The concept of TTC

- Public peer-reviewed toxicological data are only available for the minority of chemicals, and usually lacking or incomplete for emerging substances.

- For such chemicals, the Threshold of Toxicological Concern (TTC) can be used as an *alternative* approach to estimate the potential human health impact and indicate at which exposure level a negligible health risk can be assumed (Mons et al., 2013).
The concept of TTC

• The TTC is a pragmatic tool that provides conservative, screening-level exposure limits based on information on chemical structure in the absence of sufficient chemical-specific toxicological data.

• Chemicals are grouped according to their structural features and the range of toxicity of the chemicals within the group is evaluated by ranking the chemicals on the basis of their most conservative NO(A)EL value derived from animal experiments.
The initial step of applying the TTC approach is the exclusion of compounds for which no TTC could be derived. 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).
- Inorganic substances
- Metals and organometallics
- Proteins
- Steroids
- Substances that are known or predicted to bioaccumulate
- Nanomaterials
Cramer classes of chemicals I, II and III

- **Class I**: Substances with simple chemical structures and for which efficient modes of metabolism exist, suggesting a low order of oral toxicity.
- **Class II**: Substances which possess structures that are less innocuous than class I substances, but do not contain structural features suggestive of toxicity like those substances in class III.
- **Class III**: Substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups.
Derivation of a TTC

Figure 1-1. Cumulative distribution of NO(A)EL values within groups of structurally related chemicals (Cramer class I, II and III) and cut-off exposure levels representing a 5% chance of a random chemical corresponding to the respective chemical class being toxic below this exposure level (adapted from Kroes et al., 2004).
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## Proposed target values for organic contaminants in drinking water

<table>
<thead>
<tr>
<th>Compound group</th>
<th>Target value (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single genotoxic organic chemicals</td>
<td>0.01</td>
</tr>
<tr>
<td>Single (synthetic) steroid hormones</td>
<td>0.01</td>
</tr>
<tr>
<td>All other single organic chemicals</td>
<td>0.1</td>
</tr>
<tr>
<td>Total sum of genotoxic compounds</td>
<td>0.01</td>
</tr>
<tr>
<td>Total sum of (synthetic) steroid hormones</td>
<td>0.01</td>
</tr>
<tr>
<td>Total sum of all other organic chemicals</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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Conclusions (1)

- Complete absence of any trace pollutant in treated drinking water is an illusion
- Most organic substances detected lack toxicity data to derive safe levels
- Therefore, TTC-based target values for organic contaminants are proposed
- These target values correspond well with most current standards
- Useful for quality evaluations and future plans of drinking water utilities
Conclusions (2)

• TTC levels are not intended to replace substance specific toxicological risk assessment, but should only be used when toxicological information is lacking.

• The TTC can only be applied when the chemical structure of a contaminant is known and shows similarity to the substances on which the TTC levels are based, or when the substance is shown not to belong to the group of substances excluded from the TTC approach and physiochemical properties of a substances are known.
Conclusions (3)

- The TTC is a probabilistic tool, and does therefore per definition not guarantee safety for all chemicals. TTC values should be used as an early warning tool allowing a quick response when contaminants occur in (drinking) water and a reference point for policy making (priority setting for more detailed assessment of toxicity and exposure and development of analytical methodologies and monitoring programs), not as stringent target values.


In Memoriam Margreet Mons

Margreet died on 27 June 2016 at the age of 44