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EDITORIAL

Editorial: Special Issue "Effect-related evaluation of anthropogenic trace substances—concepts for genotoxicity, neurotoxicity and endocrine effects"

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The "Health-Related Indicator Value" concept

The number of non-regulated issues for drinking water will continue to rise due to (1) a further increase in the input of anthropogenic trace substances and (2) drastical improvements of methods. In fact, for the majority of the newly identified substances, there are no or only insufficient toxicological data. As a consequence, a comprehensive toxicological assessment is not possible. Nevertheless, in the context of drinking water provision, assessment of the potential health risks of such water-bound substances is indispensable. In response to this requirement, the German Environment Agency (UBA) published the recommendation "*Bewertung der Anwesenheit teil- oder nicht bewertbarer Stoffe im Trinkwasser aus gesundheitlicher Sicht*" ("Assessment of substances contained in drinking water resources that cannot (yet) or only partially be evaluated from a health-related point of view") already in 2003 after consulting the German Drinking Water Commission (UBA 2003). This recommendation is commonly known as "Health-Related Indicator Value concept" ("Health-Related Indicator Value (HRIV) concept"; "*GOW-Konzept*," "*Konzept des gesundheitlichen Orientierungswertes*"), which has proven to be a valuable tool and has been accepted by various stakeholder groups including public health authorities, water suppliers, and consumer organizations. The HRIV concept provides an instrument to estimate event-related immediate potential risks within a narrow time frame. The resulting management options ensure the security of drinking water supplies. At the same time, the harmonized approach within the administrative sphere provides legal certainty.

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Theoretical background for the Health-Related Indicator Value concept

The HRIV concept is founded on substance-related toxicological data available for human-relevant modes of action such as genotoxicity or neurotoxicity. The HRIV has been designed as a precautionary value to protect human health; in practice, an HRIV is set at a level so low that completion of data acquisition usually leads to the same or even higher values, but never to a lower value than initially set. Even though toxicological data are lacking, the $HRIV_1$ with a value of 0.1 μg/L meets the minimum requirements of §6 (1) of the German Drinking Water Directive ("Trinkwasserverordnung"; TrinkwV 2001), according to which no concern to human health may occur after life-long exposure to a potentially contaminated drinking water.

The prescribed HRIV (concentration range between 0.01 μg/L and more than 3.0 μg/L) results in a set of potential measures to minimize the concentrations of contaminants (Fig. 1). The scientific basis for this procedure becomes more robust by including recurrently the most recent toxicological experimental test strategies to extend the theoretical concept accordingly. The HRIV also meets the requirements for risk management on the basis of scientifically reliable data. Although there is enormous progress in the field of in vitro

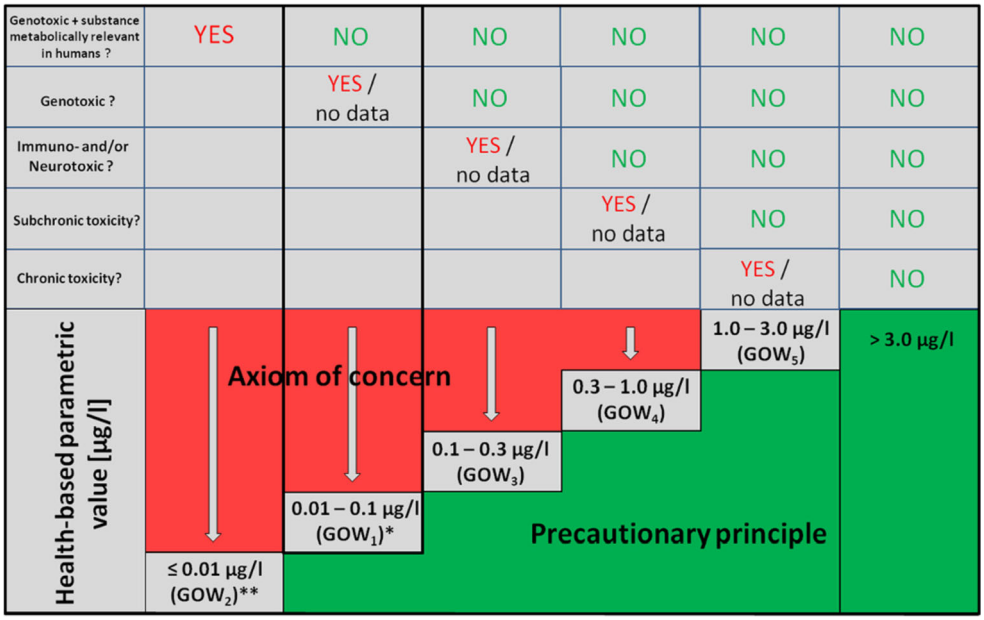

Fig. 1 Summary of the Health-Related Indicator Value (HRIV; "GOW" values depending on available toxicological data sets. * GOW_1 was set as the initial value for substances with no toxicological data available. ** Since GOW_2 was defined later than GOW_1, its number is higher although the unit value is lower (with permission from Grummt et al. 2013)

toxicology, this development has so far not been implemented into current assessment strategies used by authorities. The HRIV concept, however, tries to implement such developments by adapting the theoretical concept applied so far, which is used to derive a HRIV on the basis of conventional evaluation strategies. Thus, scientific progress finds its way into regulatory practice.

Experimental procedure of the Health-Related Indicator Value concept

Conventional toxicity assessment allows the investigation of only a limited number of substances using expensive and time-consuming animal testing. Since the results obtained are often inconsistent with human biology and pathophysiology and since the procedure gives rise to ethical concerns based on animal welfare considerations, a shift of paradigm is underway in experimental toxicology, which is described in detail in, e.g., the "Toxicity Testing in the 21st Century (Tox21)" report (National Research Council 2007). The new strategy uses in vitro testing on human cells allowing a prediction of the potential in vivo effects by identification of toxicological key mechanisms. In practice, this approach is based on "High-Throughput-Screening" (HTS) strategies (Garcia et al. 2016) and the "Adverse Outcome Pathway" (AOP) concept (Ankley et al. 2010; Russom et al. 2014; Villeneuve et al. 2014a, b). Internationally, there are extensive research programs with the following aims:

- Identification of in vitro test strategies to detect modes of action leading to adverse effects,
- detection of signature patterns of in vitro tests, which improve the prediction of in vivo effects,
- prioritization of substances for a further toxicological assessment, and
- risk assessment regarding health hazards by identification of toxicological patterns using in vitro tests.

The implementation of this strategy allows toxicity testing beyond environmentally irrelevant high-dosage studies. Substance patterns of anthropogenic trace substances identified so far provide evidence of exposure in the low-dose ranges. Taking into account that a "zero" exposure cannot be achieved in practice, the toxicological safety of anthropogenic trace substances should be characterized instead of the toxicological risk. For experimental work, this means the detection of primary modes of action.

Motivation and contents of this Special Issue

This Special Issue of *Environmental Science and Pollution Research* comprises selected papers presented at the international symposium on "Effect-related evaluation of anthropogenic trace substances—concepts for genotoxicity, neurotoxicity and endocrine effects" held at RWTH Aachen University in October 2015. The purpose of the symposium was to present the essential outcomes of the joint research project "Tox-Box—a new approach for evaluating anthropogenic trace substances in drinking water" funded by the German Federal Ministry for Science and Education (BMBF) from 2012 to 2015, and to stimulate the scientific exchange on recent cutting-edge research using effect-based methods in environmental science. Within the Tox-Box project, a holistic

approach towards a harmonized testing strategy for exposure- and hazard-based risk management of anthropogenic trace substances in drinking water to secure a long-term drinking water supply has been developed (Grummt et al. 2013). The main task of the Tox-Box consortium was to enhance the existing Health-Related Indicator Value concept (German: GOW-Konzept—Gesundheitlicher Orientierungswert) through development and prioritization of additional endpoint-related testing strategies for genotoxicity, neurotoxicity, germ cell damage, and endocrine effects. In this context, substance-specific modes of action were identified and characterized. Toxicological data collected by the 12 Tox-Box partners were evaluated and weighted to structure a hierarchical testing strategy for an improved risk assessment. A technical guidance document for exposure and hazard-based risk management of anthropogenic trace substances in drinking water is underway.

In detail, 12 communications on effect-related assessment of anthropogenic trace substances in respect to various modes of action such as genotoxicity, neurotoxicity, and endocrine effects are presented in this Special Issue, elucidating the following topics:

- Comparison of in vitro test systems using bacterial and mammalian cells for genotoxicity assessment within the Health-Related Indication Value (HRIV) concept; Prantl et al. (2018)

  This paper suggests a genotoxicity test battery consisting of (1) either the Ames fluctuation test with two tester strains, the umu test, and the micronucleus test or (2) the Ames fluctuation with five tester strains, and the micronucleus test.

- In search of a comprehensible set of endpoints for the routine monitoring of neurotoxicity in vertebrates: sensory perception and nerve transmission in zebrafish (*Danio rerio*) embryos; Stengel et al. (2018)

  This communication introduces a strategy for neurotoxicity testing on the basis of neuromast degeneration and acetylcholinesterase inhibition as enhancements of the standardized zebrafish embryo toxicity test.

- A hierarchical testing strategy for micropollutants in drinking water regarding their potential endocrine-disrupting effects towards health-related indicator values; Kuckelkorn et al. (2018)

  These authors propose a tiered test strategy for potential endocrine effects (hormonal effects on reproduction and sexual development) and inclusion of this endpoint into the HRIV concept.

- An in vitro approach for water quality determination: activation of NF-kappaB as marker for cancer-related stress responses induced by anthropogenic pollutants of drinking water; Spitta et al. (2018)

  This group discusses the suitability of an NF-kappaB-based cell assay for the detection of cytotoxicity and cancer-related stress responses for the assessment of drinking water-relevant contaminants.

- p53 Induction and cell viability modulation by genotoxic individual chemicals and mixtures; Di Paolo et al. (2018)

  This study attempts to balance cytotoxicity and reporter gene-based responses towards the use of a p53 induction cell assay for genotoxicity assessment of water contaminants.

- In vitro tools for the toxicological evaluation of sediments and dredged materials: intra- and inter-laboratory comparisons of chemical and bioanalytical methods; Eichbaum et al. (2018)

  This paper recommends the micro-EROD assay using H4IIE cells for the detection and assessment of dioxin-like contaminants in sediments and dredged materials.

- (Anti-)estrogenic and (anti-)androgenic effects in wastewater during advanced treatment: comparison of three in vitro bioassays; Gehrmann et al. (2018)

  This communication highlights the necessity of enhanced treatment of hospital wastewaters with regard to endocrine effectiveness with particular emphasis to the role of antagonists.

- Alterations in locomotor activity of feeding zebrafish larvae as a consequence of exposure to different environmental factors; Kopp et al. (2018)

  The study provides basic understanding of the impact of environmental conditions relative to non-chemical stress on zebrafish larvae behavior as a promising endpoint for neurotoxicity.

- Effectivity of advanced wastewater treatment: reduction of in vitro endocrine activity and mutagenicity but not of in vivo reproductive toxicity; Giebner et al. (2018)

  This communication is paper provides evidence that anti-estrogenic compounds and substances causing reproductive toxicity in mud snails can survive even a series of

different enhanced waste water treatments, including ozonation.

- Application of effect-directed analysis to identify mutagenic nitrogenous disinfection by-products of advanced oxidation drinking water treatment; Vughs et al. (2018)

  The authors document the suitability of effect-directed analysis for the detection and identification of nitrogen-containing disinfection by-products (N-DBPs) formed during advanced oxidation UV drinking water treatment.

- Comparative study of dioxin contamination from forest soil samples (BZE II) by mass spectrometry and EROD bioassay; Mertes et al. (2018)

  The group highlights the importance of a humic substances clean-up of soil extracts prior to EROD assays to avoid interference of non-persistent bioactive compounds with bioanalytical equivalents (BEQs).

- Identification of three mechanism-specific transcriptome signatures using *Danio rerio* embryos; Hausen et al. (2018)

  In an attempt to identify discriminative genes as markers for specific contaminants, this manuscript identifies chemical class-related transcriptome signatures in zebrafish.

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