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Commentary

The relevance of "non-relevant metabolites" from plant protection products (PPPs) for drinking water: The German view ☆

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ABSTRACT

"Non-relevant metabolites" are those degradation products of plant protection products (PPPs), which are devoid of the targeted toxicities of the PPP and devoid of genotoxicity. Most often, "non-relevant metabolites" have a high affinity to the aquatic environment, are very mobile within this environment, and, usually, are also persistent. Therefore, from the point of drinking water hygiene, they must be characterized as "relevant for drinking water" like many other hydrophilic/polar environmental contaminants of different origins. "Non-relevant metabolites" may therefore penetrate to water sources used for abstraction of drinking water and may thus ultimately be present in drinking water.

The presence of "non-relevant metabolites" and similar trace compounds in the water cycle may endanger drinking water quality on a long-term scale. During oxidative drinking water treatment, "non-relevant metabolites" may also serve as the starting material for toxicologically relevant transformation products similar to processes observed by drinking water disinfection with chlorine. This hypothesis was recently confirmed by the detection of the formation of *N*-nitroso-dimethylamine from ozone and dimethylsulfamide, a "non-relevant metabolite" of the fungicide tolylfluanide.

In order to keep drinking water preferably free of "non-relevant metabolites", the German drinking water advisory board of the Federal Ministry of Health supports limiting their penetration into raw and drinking water to the functionally (agriculturally) unavoidable extent.

On this background, the German Federal Environment Agency (UBA) recently has recommended two health related indication values (HRIV) to assess "non-relevant metabolites" from the view of drinking water hygiene. Considering the sometimes incomplete toxicological data base for some "non-relevant metabolites", HRIV also have the role of health related precautionary values. Depending on the completeness and quality of the toxicological evaluation of a "non-relevant metabolite", its HRIV is either set as 1.0 μg/l ($HRIV_a$) or as 3.0 μg/l ($HRIV_b$) for lifelong exposure. In case a HRIV would be exceeded, UBA recommends to keep on a precautionary action value (PAV) of 10 μg/l for each "non-relevant metabolite".

The $HRIV_b$ is similar to the maximal value derived by application of the TTC-concept for Cramer Class III (4.5 μg/l). The $HRIV_a$ and the PAV are similar to values in the EU-guidance document for assessing "non-relevant metabolites" in ground water, with the important difference that the drinking water PAV is not intended to be tolerated for permanent exposure.

Drinking water containing "non-relevant metabolites" below the respective HRIVs can also be considered as being sufficiently protective against toxicologically relevant oxidative transformation products which may be formed from "non-relevant metabolites" during drinking water treatment with ozone. However, even drinking water where one or several "non-relevant metabolites" are detected above substance-specific HRIVs is suited for human consumption without health risks. Only in special cases (relatively high "non-relevant metabolite" – concentrations), it could be indicated to examine the finished water for transformation products after treatment with ozone if there are no further treatment steps to eliminate or degrade polar compounds.

UBA's "non-relevant metabolite-Recommendation" from April 2008 was positively picked up in 2009 by four important stakeholders in the domain of drinking water management as part of a voluntary

☆ This is a commentary on the following articles in this issue: Toxicological potency of active ingredients in plant protection products and their "non-relevant metabolites" (Kalberlah et al.). 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 (Melching-Kollmuß et al.), and Toxicity assessment strategies, data requirements, and risk assessment approaches to derive health based guidance values for "non-relevant metabolites" of plant protection products (Dekant et al.).

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cooperation agreement. The aim of such cooperation is to limit the transport of "non-relevant metabolites" into the drinking water to the functionally (and agriculturally) unavoidable extent and insofar to meet special precautionary demands.

1. Drinking water safety and toxicology of "non-relevant metabolites"

The continued and worldwide use of plant protection products (PPP) for agricultural and other purposes justifies each reasonable effort to protect the public and the environment. Therefore, "active ingredients" (AIs) in PPPs and their "relevant" metabolites (EC, 2003; Michalski et al., 2004) are among the best-characterised substances with regard to environmental and human toxicology. On the other hand, only a small fraction of "non-relevant metabolites" can be assessed toxicologically based on a sufficient database in form of a drinking water reference (or guide) value (see article Kalberlah et al.).

Missing data do not automatically imply a health risk, but should be supplied in order to provide certainty with regard to regulations. Often this is only possible with considerable delay. In the past, two basic ideas have influenced the road to optimize consumer safety (a) availability of reliable criteria for establishing an efficient risk assessment and (b) the possibility to prioritise according to risk assessments, in order to be able to distinguish between urgent and trivial problems. Due to the large number of reported suspicious facts in the food sector, it is also necessary to establish priorities for managing and avoiding contaminants in drinking water.

In order to "separate the wheat from the chaff", two concepts to assess "non-relevant metabolites" exist: "Non-relevant metabolites" may either be provisionally assessed by application of the TTC-concept (see article Melching-Kollmuß et al.) or by a tiered experimental and exposure assessment approach (see article Dekant et al.). The first way leads to a toxicologically "safe" single "non-relevant metabolite" concentration (DWR_{TTC}) in drinking water of up to 4.5 μg/l, the latter (and more laborious) one would open the possibility to assess, on a case by case basis, any drinking water contamination by a "non-relevant metabolite" above the DWR_{TTC}.

Case-by-case risk assessments are the approach of choice to evaluate past anthropogenic contaminations of resources and environmental media during their required sanitation. A more effective (and less laborious) way to keep media and resources in future in a "sanitized" (close to nature or uncontaminated state) is to avoid cause and need for case specific assessments from the beginning. The DWR_{TTC} meets this condition with regard to "non-relevant metabolites" completely, at least at first glance. The German Federal Environment Agency (UBA, 2008) recommends an almost identical upper DWR_{TTC}, called there "health related indication value" ($HRIV_b$) of 3 μg/l. It applies to "non-relevant metabolite", which can be reliably assessed by structure/activity-analogies with well described structures, or for "non-relevant metabolites" whose data base contains at least a subchronic animal toxicity study and which, as stated in detail by Melching-Kollmuß et al., demonstrably do not indicate a potential for "critical" toxicities such as mutagenicity or carcinogenicity. For all other "non-relevant metabolites", UBA recommends not to exceed 1 μg/l.

The reason for UBA to recommend an upper HRIV of 3 μg/l instead of the slightly higher DWR_{TTC} is historical. Since 1989 (BGA, 1989) to present (BfR, 2008; Dieter, 2003; UBA, 2003), it is accepted regulatory-toxicological practice in Germany to grade recommended tolerance levels for drinking water contaminants with insufficient databases between 0.1 and 10 μg/l in steps of 3. The need of the two lower values (0.1 and 0.3 μg/l) has been excluded for "non-relevant metabolites" (UBA, 2008; UBA, 2009; article by Melching-Kollmuß et al.), whereas its $HRIV_a$ of 1 μg/l is practically identical with a corresponding maximal value of 0.75 μg/l from the EU-Guidance Document for compounds with structural elements suggestive of high toxicity (Michalski et al., 2004).

In this context, Melching-Kollmuß et al. state some "confusion" due to a 100%- instead of a 10%-contribution of the general level of toxicological concern (1.5 μg/d and person) via drinking water. It is, however, not imperative to always assign 10% of a TDI or ADI to daily drinking water consumption (*see also very last paragraph of part E of this commentary*). This might even be a incorrect approach as was pointed out for "non-relevant metabolites" by Dekant et al. For example, many side products of drinking water disinfection are demonstrably ingested exclusively from this pathway. The same knowledge applies to some metals as ingested in form of corrosion products from drinking water installations or as natural constituents of certain untreated raw/drinking waters.

The 10%-approach for "non-relevant metabolites" would be at best an argument in favour to apply the general precautionary limit value for PPPs and their relevant metabolites, which is 0.1 μg/l, also to "non-relevant metabolites". This would, from a toxicologists view, be admittedly much too conservative. On the other hand, the German Drinking Water Advisory Board has given good reasons to support a similar view from the point of drinking water hygiene when it nominated the group of "non-relevant metabolites" in this context just as one of several groups of "relevant contaminants" of drinking water which should be regulated on a voluntary basis to this limit value (TWK, 2007).

This translates to the **parts B to F** of this commentary. They cover different aspects of socially consensual assessment of "non-relevant metabolites" in drinking water at and below merely health related indication values.

2. Precautionary principle and axiom of concern within the context of protecting drinking water from environmental contaminants

According the seventh article "Water" of the German Protection Against Infection Act (*Infektionsschutzgesetz*, *IfSG*), §37 which is one of two main footholds of the German Drinking Water Ordinance of 2001 (TrinkwV 2001), "water for human use (...) must be of such quality that there is no reason to fear any damage to human health, particularly through pathogens, being involved in its consumption or use".

The statement "free of concern", legalized in the IfSG, expresses a quality requirement, which demands not only the prevention of scientifically quantifiable and accordingly known risk potentials, but also precautionary measures against those risk potentials which can be expected on the basis of plausible risk assessments and appear to be greater then zero although they cannot be quantified (yet).

Thus, this so-called axiom of concern (*Besorgnisgrundsatz*) requires a drinking water which, for principle of precaution, has a better quality and higher purity than could be described toxicologically by single substance analysis and for life-long consumption. This requirement, for example, must also be satisfied by a drinking