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Comments on "Human health risk assessment of pharmaceuticals and personal care products in plant tissue due to biosolids and manure amendments, and wastewater irrigation"

The occurrence of pharmaceuticals and personal care products (PPCPs) in the agricultural environment is of great concern; hence the risk for human health should be thoroughly assessed. The article "Human health risk assessment of pharmaceuticals and personal care products in plant tissue due to biosolids and manure amendments, and wastewater irrigation" by Prosser and Sibley (2015) reviewed 24 papers in order to assess the concentrations of PPCPs in edible tissue of plants grown in soil amended with biosolids or manure or irrigated with wastewater. They concluded that the concentration of the majority of PPCPs in the edible plant tissue represents a *de minimis* risk to human health.

In this commentary, we argue that the review by Prosser and Sibley (2015) did not provide a comprehensive assessment of the health risks associated with exposure to PPCPs through the consumption of edible crops. The article presents data for only 12 different plant species and without any link to dietary data; since the crops were grown under very different experimental conditions the data cannot be directly compared or generalized; and much of the data were collected from studies which were not conducted under typical agricultural conditions. Moreover, Prosser and Sibley (2015) did not use strict health risk assessment uncertainty factors and therefore their calculated acceptable daily intake (ADI) values were high. Also the authors ignored health risk assessments reported in the reviewed studies focusing only on their own risk assessment. In addition, some errors in collected data and calculations were found. Lastly, the presence of metabolites of PPCPs in edible crops was not considered though metabolites of PPCPs can be potentially more problematic than the parent compound. Our main points of criticism are listed below.

We believe that the current data are insufficient to support a comprehensive human health risk assessment for the studied subject.

1. Crop growing conditions

Several of the reviewed studies report uptake and fate of PPCPs under growing conditions that are not relevant in terms of agronomical practices. For example, Aryal and Reinhold (2011) examined uptake of triclosan and triclocarban by pumpkin, zucchini, and switch grass which were grown in 14.7 × 30 cm soil columns. Prosser et al. (2014) used deionized water to irrigate radish, carrot, and soybean grown on soil amended with biosolids. Such cases are not only unrealistic in terms of commercial agronomic practices but they may also foster unrealistic scenarios in terms of the biological, physical and chemical processes that PPCPs may undergo in the soil that in turn will affect their bioavailability and uptake. Furthermore, several of the reviewed studies failed to report proper methodology (Pannu et al., 2012), detection limits (Gottschall et al., 2012) or presented results where the control was either equal to or even higher in PPCP concentration than the treated plants (Sabourin et al., 2012). Critical review of the cited articles is missing.

Over half of the presented values regarding the accumulation of PPCPs from manure amended soils were taken from 2 papers that largely failed to show a significant difference between the control and the treated plants (Bassil et al., 2013; Kang et al., 2013). Bassil et al. (2013) used an ELISA kit to quantify the PPCPs. Results of this study showed that all PPCPs were detected in the control as well as in the treated plants (differences were significant for only one compound in one out of three crops). Kang et al. (2013) which also based their analysis on ELISA kits, reported concentrations that were near the limit of quantification, most PPCP concentrations in manure treated crops were not significantly different than the control, and no extraction recovery was performed for the different crops. The lack of significant difference in both of these studies requires questioning regarding the validity of such studies for risk analysis.

In the section addressing the accumulation of PPCPs in plants grown in soils that were irrigated with wastewater, only two studies were thoroughly discussed (Calderon-Preciado et al., 2013; Goldstein et al., 2014). Furthermore, the data do not properly describe PPCP uptake by plants under wastewater irrigation. Although Goldstein et al. (2014) examined PPCPs in crops irrigated with real treated wastewater, the data presented from Goldstein et al. (2014) by Prosser and Sibley (2015) referred to plant uptake from spiked freshwater irrigation. Thus 8 out of the 32 reported compounds (bezafibrate, caffeine, gemfibrozil, ketoprofen, lamotrigine, metoprolol, sildenafil and sulfapyridine) do not represent wastewater-derived PPCP uptake. In the spiked or non-spiked treated wastewater irrigation treatment most of these compounds were reported to be not taken up by the plant (Goldstein et al., 2014). The review included additional studies that examined crop uptake with spiked freshwater irrigation (Marsoni et al., 2014), a scenario which does not represent irrigation with treated wastewater as demonstrated by Goldstein et al. (2014).

2. Human health risk assessment

Accepted daily intake (ADI) level is typically calculated by determining the dose of the no observed adverse effect level (NOAEL) (Renwick, 1995; Larsen, 2006). The ADIs used in the current review are based on minimum therapeutic dose (MTD), the lowest concentration that induces a desired therapeutic effect among target populations. When the NOAEL is unavailable, several studies used the MTD with an appropriate safety factor (1000 for most compounds, Table 1, Prosser and Sibley, 2015) in order to estimate the safe level of exposure (Bull et al., 2011; World Health Organization, 2011). Uncertainty factors are applied to the NOAEL in order to account for a lack of information on the chemical being assessed (Renwick, 1995). As recommended, the assessment by Prosser and Sibley (2015) calculated risk uncertainty factors for 1) differences in response between humans (compared to the tested animals), 2) potential sensitivity of subgroups of the population (*i.e.*, children and infants), and 3) the lowest daily therapeutic dose not

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being a level that represents NOAEL. However, the assessment of human health risk should take into account additional unknown risks and thus apply additional uncertainty factors for PPCPs, *e.g.*, potential genotoxicity, metabolism or exposure to mixture of PPCPs (Renwick, 1995; Kroes et al., 2005; Larsen, 2006).

Compounds with higher toxicity should have an additional safety factor (World Health Organization, 2011). Prosser and Sibley (2015) provided an additional uncertainty factor only for endocrine disrupting compounds, testosterone and progesterone, failing to consider 16 additional compounds listed in Table 1 (Prosser and Sibley, 2015) that have potentially genotoxic properties. These are: 10,11-epoxycarbamazepine, ambrettolide, chloramphenicol, chlortetracycline, ciprofloxacin, lamotrigine, meprobamate, norfloxacin, progesterone, streptomycin, sulfamethazine, sulfamethoxazole, sulfapyridine, tetracycline, triamterene, tylosin and virginiamycin. The fact that the genotoxic properties of a large portion of examined PPCPs were not taken into account gravely underestimates the calculated health risk.

3. Metabolites of PPCPs

Prosser and Sibley (2015) did not consider the metabolism of PPCPs in crops. The issue of metabolism has been addressed in several PPCP plant uptake studies (Huber et al., 2009; Macherius et al., 2014; Goldstein et al., 2014; Malchi et al., 2014; Bartha et al., 2014) as well as in the health risk study of pharmaceuticals in drinking water (Houeto et al., 2012). Wu et al. (2010, 2012) reported that the anticonvulsant drug carbamazepine was detected in leaves of soybean and tomato but not in the bean of the soybean or in the tomato fruit. Results from Goldstein et al. (2014) provide sufficient evidence that although the parent compound was not detected accumulation of metabolites in the fruit may occur.

Metabolites, such as methyl-triclosan derived from triclosan or epoxy-carbamazepine derived from carbamazepine, are potentially more toxic than the parent compound and have been found at significantly higher concentrations than the parent compounds (Farré et al., 2008; Goldstein et al., 2014; Malchi et al., 2014). Hence, PPCP metabolism warrants discussion in assessing human health risk of crops and certain PPCPs should have an additional uncertainty factor, especially if the PPCP's metabolites possess higher biological activity than that of the parent compound.

4. Exposure to a mixture of PPCPs

Prosser and Sibley (2015) implemented a single compound approach to estimate risk although they allude to the importance of examining the cocktail effect of PPCPs and show that the sum of the hazard quotients of different PPCPs surpasses the 0.1 threshold. The follow-up discussion concludes that there is too much uncertainty regarding the interaction of drugs. This type of uncertainty should not be ignored as part of the risk assessment and rather should be included as an additional uncertainty factor in the ADI calculations (Table 1, Prosser and Sibley, 2015). Although the authors briefly state that the additive effect would give their assessment a different conclusion, they downplay the higher hazard quotient by eliminating the higher values stated in their review as not being environmentally relevant or stating that exposure is rather a function of the vegetables a person consumes. McClellan and Halden (2010) detected 38 different PPCPs in biosolids sampled from 94 wastewater treatment plants across the United States. All biosolids contained at least 26 different PPCPs. Similarly, Jelic et al. (2011) reported the presence of 29 PPCPs in effluent water in Spain. In studies that have examined the uptake of PPCPs by plants grown under field conditions, compounds have been applied as mixtures resulting in more than one PPCP being detected in a single crop (Wu et al., 2010, 2012; Calderon-Preciado et al., 2013; Goldstein et al., 2014; Malchi et al., 2014). Thus, the article conveys the impression of safety, with a *de minimis* risk, when ignoring that exposure to PPCPs is always as mixtures and not as single compounds.

5. Review of health risk assessments conducted by reviewed articles

Several of the studies cited by Prosser and Sibley (2015) provide their own health risk assessment; however none of these assessments were noted or referred to. For example, Wu et al. (2014) compared crop concentration to the concentration of a single medical dose; Aryal and Reinhold (2011) compared concentration to the NOAEL; Boxall et al. (2006) and Dolliver et al. (2007) compared crop concentrations to ADI levels provided by the World Health Organization; Carter et al. (2014) calculated the ADI based on the minimum therapeutic dose with an additional 100 uncertainty factor; and Malchi et al. (2014) used the threshold of toxicological concern (TTC) approach. None of these assessments were discussed.

Boxall et al. (2006) emphasized that the application of the ADI obtained from the World Health Organization may result in the underestimation of associated health risk due to the formation of metabolites of these compounds, the effect of PPCP mixtures and the issue of chronic exposure to PPCPs. Malchi et al. (2014) used the TTC approach as a conservative estimate that applies uncertainty factors based on the NOAEL from studies on compounds sharing similar structural characteristics as the target compound. TTC is useful to assess risks for substances present in food at low concentrations and lacking toxicity data (Kroes et al., 2004).

6. Errors in data

Inaccurate reporting of datasets and incorrect calculations provided misleading results that fail to accurately illustrate a reliable risk assessment. Data presented in Table 2 (Prosser and Sibley, 2015) contain dry weight concentrations of PPCPs in the edible plant tissue. However, the data in the original papers were not always presented as dry weight concentrations. For example, the concentration of 10,11-epoxycarbamazepine in carrots, reported by Malchi et al. (2014) was reported as ng/g fresh weight, but Prosser and Sibley (2015) present it as ng/g dry weight. In this case the conversion factor from dry to fresh weight is calculated using the percent dry weight, $\frac{FW\ \ concentration}{dry\ \ matter\ \ fraction} = \frac{0.2448}{0.18} = 1.36\frac{ng}{g}\ DW$. The same error was made for 9 additional compounds (ambrettolide, carbamazepine, clofibric acid, diclofenac, flunixin, galaxolide, ibuprofen, naproxen and tonalide) which were reported for fresh weight concentrations by Calderon-Preciado et al. (2013) but taken as dry weight concentrations in the review. This mistake results in much lower ADIs for vegetables crops that often range in 85–95% water content. For example Calderon-Preciado et al. (2013) found the highest concentration of flunixin in lettuce (~95% water) to be 83 ng/g fresh weight, and the dry weight concentrations are: $\frac{FW\ \ concentration}{dry\ \ matter\ \ fraction} = \frac{83}{0.05} = 1660\frac{ng}{g}\ DW$. Applying such concentrations to the current review would indicate that a human health risk exists for PPCPs. A closer examination of the data reveals that flunixin was only detected in 2 out of 9 samples, further questioning the applicability of the data reported. The data for the remaining compounds (Table 2) were reported for dry weight concentration, hence part of the data were reported for fresh weight and the other part for dry weight. This requires readers to refer to every cited article in order to be able to understand the data reported.

Similar misrepresentation of the reported data was present in the biosolid derived and manure derived sections. Dry weight concentrations are always higher than the fresh weight hence the PPCP intake to exceed ADI is considerably underestimated. Furthermore, the data do not always accurately reflect the worst case scenario. The difference between values of concentration and index calculated for dry and fresh plant weight can dramatically change the worst case scenario for different crops with varied PPCP concentrations and water content.

The "adult intake to exceed ADI (g/day)" was estimated using concentrations calculated for dry weight rather than fresh weight. The ADI should present fresh weight values because people buy and consume

fresh vegetables and fruits. The "ADI" values (Table 1; Prosser and Sibley, 2015) are incorrect and should be calculated for the fresh weight of plants.

The relevance of the estimated daily intake (EDI) values is also questionable. This index should be calculated based on consumption data available for adults and toddlers separately. The use of the value 2.8 cups per day ignores different consumption habits by adults (2.9 cups/day) *versus* toddlers (1.45 cup/day) (National Cancer Institute, 2005). The EDI was calculated assuming that all people consume 2.8 cups of a single vegetable per day, which does not represent a realistic scenario. Furthermore, the value presented in this review acquired from the U.S. based National Cancer Institute is only valid for the United States whereas different countries have different dietary consumption habits of fruits and vegetables. Generally, the relevance of the data, discussion and conclusions of this review are highly questionable.

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