Letter to the Prof. José L. Domingo, Editor-in-Chief of *Food and Chemical Toxicology* regarding the recent paper "Refined assessment and perspectives on the cumulative risk resulting from the dietary exposure to pesticide residues in the Danish population" by Martin Olof Larsson, Vibe Sloth Nielsen, Niels Bjerre, Frank Laporte, Nina Cedergreen, Food and Chemical Toxicology 111 (2018) 207–267, https://doi.org/10.1016/j.fct.2017.11.020.

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Abstract

Larsson and coworkers recently presented a study in *Food and Chemical Toxicology* on the cumulative risks to the Danish population from dietary exposure to pesticide residues. They base their analysis on food monitoring data, spray journals, controlled field trials and food consumption data in the Danish population. A cumulative hazard-index (HI) approach is then used to estimate the overall risk from pesticide exposure, an approach well established in the literature. Based on an HI of 13-44%, the authors conclude that adverse health effects due to pesticide residues are “very unlikely” and equivalent to “1 glass of wine every seventh year”. Unfortunately, the paper fails to put the limitations of the underlying data and the applied methodology in context and it misinterprets the use of Assessment Factors in chemical safety assessment. The comparison of population-wide life-long involuntary exposure to pesticides with individual, time-limited, voluntary alcohol consumption is misleading, in particular in view that children are identified as the most vulnerable sub-population.

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Dear Prof. Domingo,

Larsson and coworkers recently presented a study in *Food and Chemical Toxicology* on the cumulative risks to the Danish population from dietary exposure to pesticide residues. They base their analysis on food monitoring data, spray journals, controlled field trials and food consumption data in the Danish population. A cumulative hazard-index (HI) approach is then used to estimate the overall risk from pesticide exposure, an approach well established in the literature. Based on an HI of 13-44%, the authors conclude that adverse health effects due to pesticide residues are “very unlikely” and equivalent to “1 glass of wine every seventh year”. We find these conclusions overly simplistic and seriously misleading.

The study estimates that the pesticide exposure of Danish consumers equals between 13% (adults) and 44% (children) of the cumulative acceptable daily intake (ADI). For adults with high fruit and vegetable consumption the exposure increases to 22-26% of the ADI. Unfortunately, the authors do not provide information for children with a high vegetable consumption, although the data from adults indicate that those children are most at risk from pesticide residues in their diet.

All those values represent averages. The study therefore does not at all answer the far more important question of how many Danish adults and children are actually exposed to pesticide levels exceeding the cumulative ADI. That is, the study does not provide any estimates on the underlying exposure and risk distributions, which would require a probabilistic assessment. The corresponding approaches are well established in the literature, also *Food and Chemical Toxicology* devoted a whole special issue already in 2015 to this topic (Barlow & Boon, 2015).

We are aware that a fully quantitative probabilistic assessment is not easily implemented. However, the study by Larsson et al. does not even include a rough semi-quantitative discussion of the underlying

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uncertainties and possible biases in the underlying data and their approaches. Ambrus & Szenczi-Cseh (2017), for example, provide an overview of the size of the various uncertainty drivers in dietary pesticide exposure assessments that could have been use for this purpose (see also the discussion in Kennedy et al., 2015). When simple, deterministic models as the one in the Larsson et al study are used, their limitations and potential biases need to be clearly acknowledged before drawing broad-sweeping conclusions.

Secondly, the authors misinterpret the concept of assessment factors (AFs) when arguing that the presented risk estimates are conservative because the ADI values of the individual pesticides have inbuilt “safety margins”. These AFs merely compensate for the uncertainty and variability in the extrapolation from animal data to human health impacts and for the increased sensitivity of certain individuals. They certainly do not account for cumulative effects (Martin et al., 2013).

In addition, the HI approach is sensitive to the criteria used for selecting the individual ADI values. For example, the selected ADI value for the most influential compound in the study by Larsson et al. (aldrin/dieldrin) is 0.0001 mg/kg. This value was developed by the Joint Meeting for Pesticide Residues in 1992. A decade later (2002) the Agency for Toxic Substances and Disease Registry (ATSDR) adjusted the value to only 0.00003 mg/kg, a reduction be a factor of 3. Just by selecting another ADI value the relative contribution from aldrin/dieldrin would increase three-fold.

Thirdly, the hazard index method used by the authors assumes an additive toxicity of the components in the mixture. However, especially acetylcholine esterase inhibitors and azole fungicides seem to be often causing more-than-additive, synergistic mixture toxicities (Cedergreen, 2014). These compounds make up a sizable fraction of the pesticides found in the Danish diet (at least Prothioconazole, Epoxiconazole, Propiconazole, Tebuconazole, Difenoconazol, Chlorpyrifos, Dichlorvos, Diazinon, Ethoprophos). The presence of these compounds therefore might indicate that the hazard-index method systematically

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underestimates the joint toxicity of the encountered pesticide mixtures. It is therefore somewhat surprising to see that the issue is not even discussed as a potential source of bias in the paper.

Fourthly, we find the concluding statement that “The hazard index for pesticides for a Danish adult was on level with the hazard quotient for alcohol for a person consuming the equivalent of 1 glass of wine every seventh year” nonsensical. Although the authors have already slightly revised their statement in a corrigendum to their paper (Larsson et al., 2018), the comparison with ethanol is simply irrelevant *per se* from a public health perspective. In particular because children are identified as the subpopulation put most at risk from pesticide exposure.

Even if one (reluctantly) follows the authors on their path to comparing risks of population-wide, life-long, involuntary pesticide exposure with individual, time-limited, voluntary alcohol consumption, the “theoretical ADI” of 17.3 mg/kg bodyweight and day that is suggested by Larsson and his colleagues still artificially reduces the alcohol ADI by a factor of five: The oral DNEL (Derived No Effect Level, which is ECHA’s terminology for an ADI) for alcohol in the referenced ECHA dossier is 87 mg/kg bodyweight and day (ECHA, 2018).

The “theoretical ADI” by Larsson et al. simply disregards the statement in ECHA’s dossier that for alcohol the use of the standard uncertainty factor of 100 “is considered excessive” (ECHA, 2018). That is, during the construction of their “theoretical ADI” the authors conveniently ignore that uncertainty factors are always adjusted according to expert judgement and the knowledge available for the compound in question. In sharp contrast, this is of course considered for all the pesticide ADI calculations.

In summary, the comparison of the cumulative pesticide hazard index with a heavily beautified construct that the authors label a “theoretical ADI for alcohol consumption” only seems to serve the purpose of downplaying the relative pesticide risks, in a comparison that does not make too much sense to begin with.

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Finally, it should be stressed that the study results certainly need to be put into the broader perspective of public health protection. The study shows that an average Danish child receives 44% of its total ADI from ingesting plant-based food items alone, a value that is most likely even higher for children growing up on a vegetarian diet. These estimates ignore any pesticide intake via non-oral routes, i.e. bystander exposures and exposures from pesticide application in school gardens, sport facilities and parks, private gardens and on indoor plants at home. Additionally, previous studies have shown considerable exposure of the Danish population, especially children, to other hazardous chemicals, e.g. phthalates and persistent organohalogen pollutants (e.g. Søeborg et al., 2012). Taken together, population-wide total exposure to pesticides and other hazardous chemicals is most likely at a level that gives cause for concern. Rather than "showing that pesticides are very unlikely to pose a risk to the health of Danish consumers" the study illustrates the need of considering cumulative effects when determining safe exposure levels, in particular for children.

Finally, we noticed that *Food and Chemical Toxicology* requests their authors to fill in a declaration on their conflicts of interest. But surprisingly, although four authors are directly employed by Bayer Crop Science, only Dr Laporte declares a potential conflict interest, due to his work as an expert in the residue expert group of the European Crop Protection Association. All other authors declare "no conflicts of interest to disclose". This seems in clear violation of the request in the journal's author guidelines to declare "All financial relationships with any entities that could be viewed as relevant to the general area of the submitted manuscript" and to declare "Any other relationships or affiliations that may be perceived by readers to have influenced, or give the appearance of potentially influencing, what you wrote in the submitted work."

Kind regards

Prof. Thomas Backhaus, University of Gothenburg

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References

Ambrus Á., Szenczi-Cseh. J. 2017. Principles of Estimation of Combined Uncertainty of Dietary Exposure to Pesticide Residues. EC Nutrition, 7, 228-251.

Cedergreen, N. 2014. Quantifying synergy: a systematic review of mixture toxicity studies within environmental toxicology. PloS one, 9(5), p.e96580.

Martin, O.V., Scholze, M., Kortenkamp, A. 2013. Dispelling urban myths about default uncertainty factors in chemical risk assessment–sufficient protection against mixture effects? Environmental health, 12(1), p.53

ECHA (2018). Registration Dossier for Ethanol, Downloaded 21.2.2018 https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/16105/7/1

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Kennedy, M.C., van der Voet, H., Roelofs, V.J., Roelofs, W., Glass, C.R., de Boer, W.J., Kruisselbrink, J.W. and Hart, A.D., 2015. New approaches to uncertainty analysis for use in aggregate and cumulative risk assessment of pesticides. Food and Chemical Toxicology, 79, pp.54-64.

Larsson, M.O., Nielsena, V.S., Bjerre, N., Laporte, F., Cedergreen N. 2018. Corrigendum to “Refined assessment and perspectives on the cumulative risk resulting from the dietary exposure to pesticide residues in the Danish population”. Food and Chemical Toxicology, 113, 345-346

Barlow, S.M., Boon, P.E. 2015. Toxicity testing and model development for estimating cumulative and aggregate exposure to pesticide residues in Europe. Special Issue in Food and Chemical Toxicology

Søeborg, T., Frederiksen, H., Andersson, A.M. 2012. Cumulative risk assessment of phthalate exposure of Danish children and adolescents using the hazard index approach. International journal of andrology, 35(3), 245-252.

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