Author’s response to reviews

Title: Human health implications of organic food and organic agriculture: A comprehensive review

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Version: 1 Date: 25 Sep 2017

Author’s response to reviews:

We thank the reviewers for their efforts, and for their constructive and relevant comments. Before responding to the individual comments in detail below, we would like to highlight the following minor changes to the manuscript that we have implemented:

(1) Regarding the fungal toxin DON in cereals: there is a fresh EFSA risk assessment for DON, showing that the mean dietary exposure for several population groups is above the tolerable daily intake (TDI). Therefore, an effect of agricultural practices on DON content of cereals (being the main source of DON to humans) has gained in relevance, and we decided to strengthen this point with 5 additional lines of text, and 2 additional references.

(2) We have updated a key reference for the antibiotics section: In the end of July, EFSA released an update of their 2015 report on the link between antibiotic use in humans and animals and the development of antibiotic resistance in bacteria. Overall, EFSA concludes that the link between use and development of resistance has been confirmed and strengthened (http://www.efsa.europa.eu/en/press/news/170727-0). We feel that it is appropriate to refer the interested reader to the updated report. We update a few numbers accordingly but this does not change the conclusions regarding antibiotic resistance.
We provide the revised manuscript in one clean version, and one version with tracked changes.

Reviewer reports:

Reviewer #1: This review is broad in scope and looks at health implications of organic food and organic agricultural systems. Specific topics, e.g. nutrient composition of organic vs conventional food crops have been reviewed before, but this review includes a wide range of implications of organic farming and organic food consumption. From the author contributions it appears that this was a very collaborative piece of work, however I think the structure and ordering could be improved. I think what would help is if the authors stated very clearly in the background section, what topics they were going to cover, and in the order that they cover them in the main body of the review. At the moment in the third paragraph the authors state they will review 1) plant protection strategies and human pesticide exposure... Human pesticide exposure is the 4th section of the review. I think rather than making broad statements here, if you could very specifically state what you will cover and in the order that you will cover it, it will help make to make the manuscript easier to follow. At the moment the background doesn't seem to closely align with what is covered in the body of the review.

->We have restructured and in part reworded the introduction/background in order to improve the flow and structure, and in order to clarify the scope.

I see that for this journal there is no methods section for a review, however I wondered if there were anywhere that you could briefly describe your search strategy. I don't know of any articles that you have missed but I would like to know how you searched for studies.

->We have added a brief description of our search strategy in the end of the Background

Specific comments for various sections are as follows:

1. Organic food consumption and health - human studies, page 4, lines 29-31. Compliance assessment in intervention studies may be difficult, but this is unlikely to be the limiting factor in conduction an intervention study. Such a study would be very expensive, as it would need to recruit thousands of participants, and follow them over many years. In fact, assessing compliance is really similar to measuring the exposure (organic food consumption) in cohort studies, which is also challenging.

->We fully agree with this comment. The sentence has been modified.
2. Page 5, lines 4-7. I think it is worth mentioning here that this is most likely to be due to residual confounding (or possibly multiple comparisons/testing). Is there any biological mechanism whereby organic vegetables would reduce risk of pre-eclampsia?

-> We have now added information that not organic food preference overall, but specifically organic vegetable consumption, is associated with the lower risk for pre-eclampsia. This information enables the reader to interpret the reported OR accordingly (as a subgroup analysis, with the associated issue of multiple comparisons). The issue of residual confounding, with special regard to dietary and lifestyle factors of relevance in the context of preference of organic food, is discussed elsewhere in this section, and is generally relevant for all studies reported here (although individual studies differ in the rigour that they address this issue with – we now highlight the Kesse-Guyot 2017 paper in this respect). – All of the observational studies reported in this section, including the pre-eclampsia study, feature some discussion on plausibility and potential mechanisms of findings.

Due to space limitations and not to discuss this specific study in detail (compared to the others), we choose to refer to the general discussion of residual confounding.

3. page 5, lines 32-26. Should specify the lower risk of NHL was observed in those that reported usually or always consuming organic food compared to those who reported never consuming organic food.

-> As requested, we have now added this detail.

4. Organic food consumption and sustainable diets. A lot of the discussion in this section doesn't seem to be relevant to to the question of organic food vs conventional food. I think the first sentence is relevant, and could be expanded upon, what are the areas where organic agriculture is better than conventional, where is it the same, or worse? The discussion about how organic food consumers eat more vegetables and less meat, and these diet patterns are associated with reduction in disease....I don't find this relevant. The review is about organic food vs conventional food, this is veering into the correlates of organic food, and is not about the direct effect of the production system. I also can't see the relevance of stating that Mediterranean Diets/Nordic Diets are similar to the diets of people who eat organic food, and these diets are associated with reduced risk of disease, and lower carbon footprint. This is really straying from the aim of the review to directly compare organic food and convention food/food production systems. The second paragraph is a very important point, and I think this point should be moved up in the order because it applies to the section on organic food consumption and human health.
-> We agree with the points of this reviewer that this section sticks out a bit. However, we find it relevant to put findings relating to production system and health into a wider context of how food system and health are related. (Food system – simplified as production + consumption.) This also relates to the first sentence of the “background” section, stressing the importance of development towards sustainable food systems.

We follow the suggestion of this reviewer and move the part on correlates of organic food consumption into the section on human studies. Another part is moved to the discussion in order to provide a perspective wider than production system and put our findings into the context of sustainable diets.

5. Page 13, line 40-47. The concluding sentence that there is uncertainty with the IQ cost implications calculation but that it is probably an underestimate because it is one group of pesticides...I get your point that it is not all pesticides, but the main problem is that the model assumes causality and certainty that organophosphate exposure does reduce IQ, which is not entirely convincing given that it is not supported by the PELAGIE cohort in France (albeit with a relatively lower organophosphate exposure in that cohort).

-> Your point is correct, that causality cannot be fully proven in the absence of clinical trials. Still, developmental neurotoxicity is well established in laboratory models, and the US epidemiological studies are in mutual agreement at similar exposure levels, and the French study at lower levels fits into this pattern. The conclusions are in agreement with other recent reviews, and we therefore believe that our summary is appropriate and balanced, as we have now explained in further detail.

Page 15, line 15. A reference is needed for the statement about the detrimental effects of cadmium.

-> We have added a reference supporting this point.

Page 16, lines 47-49, and page 17, lines 23-40. The reference #195 describes in detail an important point which should be mentioned in this section, which is that diet composition has less impact on the fatty acid composition of meat in ruminants because the microorganisms in the rumen metabolise the unsaturated fatty acids and the major fatty acid leaving the rumen is C18:0. For the paragraph on page 17 describing the nutritional content of organic vs conventional meat, when summarising the data it would be useful to distinguish between ruminants and non-ruminants, because of this major difference in net absorption of types of fatty
acids. I would expect differences in omega-3 content between organic and conventionally-farmed ruminants to be less than for non-ruminants.

- It is correct that n-3 metabolism and transfer to meat is different for ruminants and monogastric animals. However, the relationship n-3 in the feed and n-3 in the meat is generally monotonous for both. The absolute n-3 content of meat would be expected to be lower for ruminants under the assumption of similar feed n-3 content, due to microbial activity in the rumen (see also table 1, Woods 2009, original ref #195, roughly confirming this). However, the ratio of n-3 concentration in organic compared to conventional meat would not generally be expected to differ between monogastric and ruminant animals. In addition, the ratio on feed n-3 content in average organic compared to conventional production may be different for different animal species.

The meta-analysis by Srednicka-Tober specifies the total n-3 content to be 47% higher in organic meats. However, the numbers of studies for each species is low and there is no apparent trend visible for ruminants vs monogastric animals. Given the scarcity of data, we feel that it would be difficult to add further differentiation for different types of animals. However, we added a sentence highlighting these uncertainties.

Page 19, line 51. A reference is needed for this statement.

- We reworded slightly and backed up with references.

Page 20. I think this section could benefit from some restructuring. The organisation of ideas into paragraphs is not always logical. The first three paragraphs on page 19 seem to all be making the point that there is probably less antibiotic resistance on organic farms. One suggestion for re-ordering that I think would make more sense an order is to start page 19 with the paragraph "Previously...in has been postulated...", then 'Resistant bacteria may be transferred with the production chain..' and then "In pig production, particular attention has been paid...'.

- Thanks. We implemented the suggested change.

Page 20, lines 4-6. The estimates of MRSA being found in 30%-55% of pigs tested - is that on conventional farms?

- We have clarified this. The number refer to all pigs, of which conventional ones are >99%.
Discussion, page 20-21. This is well written and does a good job of tying all the components of the review together. There are no references in the first three paragraphs, and some of these statements need to be supported by references. Again, I don't think it is relevant to this review that people who eat organic food are likely to have a lower risk of disease because eating organic food is correlated with other beneficial behavioural and lifestyle factors. The review should be focussed on whether organic food or organic agricultural productions confers direct effects on health.

-> We have added some key references to this section, while trying to avoid duplication of the body of the manuscript.

We maintain that it is relevant to put health effects of the production system into a wider perspective of effects of diets and the food system, but agree that the discussion (and not the body of the article) are the right place to do this.

Page 23, line 35. Would be helpful to specify "Nutrient composition differs only minimally...."

-> We have made the suggested change, and reworded slightly to avoid collecting phenols and cadmium under the term “nutrients”.

Reviewer #2:

Excellent coverage of the literature and key issues.

The quality of language in the manuscript is generally good but could be tightened up a bit in some sections e.g. Association between organic food consumption and health: findings from human studies; the final paragraph under Organic food consumption and sustainable diets (P6 L15...); P15 L 4-5.

It may be beneficial to break some of the longer sentences down to improve readability e.g. P 5 L38-45.

-> We have implemented the suggested changes.

Table 1 data appearing twice?

-> This must be some technical error – in our submitted Word file, it is only once but in the pdf twice.
P 10 With regard to the following statement I think the presence of detectable pesticide residues in 13.8% of organic food samples might be higher than most consumers would expect. What are the organic standards in the EU regarding organic products found to exceed certain residue levels? I believe in Australia detections >10%MRL cannot be sold as 'organic'


"On average over the last three available years, EFSA reports pesticide residues below Maximum Residues Levels (MRL) in 43.7% of all and 13.8% of organic food samples. A total of 2.8% of all and 0.9% of organic samples exceeded the MRL, which may be due to high residue levels or due to low levels but unapproved use of a particular pesticide on a particular crop [82-84].

->We have added some details to clarify this. Indeed, exposure relative to toxicological reference values (ARfD and ADI) is more relevant from a human health perspective than detection below or above MRL. Acute and chronic risk assessments are scarce but we discuss the existing ones.

P17 L32 consider 'feeding regimens' rather than 'feeding regimes'

->Thanks, we have made this change at several places in the manuscript

P18 L23-27 needs clarification

->The origin of ruminant trans fatty acid is briefly specified a few paragraphs further up – 4th paragraph of “Animal-based foods” section. We think that this information is sufficient for this review. The interested reader will find the references, discussing the synthesis of these fatty acids in the rumen and their potential relevance (also relative to industrial trans FAs) for humans.

P19 Regarding the use of antibiotics for therapeutic purposes in organic livestock... what are the EU organic standards? According to Australian standards, antibiotics can be used in organic livestock but there are restrictions on selling that animal as 'organic' or growing organically certified crops on the land.


->We have added a specification of this issue.
Reviewer #3: This is an outstanding article that indeed provides a comprehensive overview of the current state of the research into the health impact of organic food. As there are very few direct human studies on the health impact of organic food the authors have had to make conclusions based on extrapolations from epidemiological and animal studies and they have done a commendable job in reviewing the existing literature.

Their conclusions however are likely to underestimate the benefits of organic food consumption as current risk assessments for pesticides do not adequately address the risks of exposure to combinations or for carcinogenesis, endocrine-disruption or neurodevelopmental toxicity.

->We have added the sentence “Also, gaps in the regulatory approval process of pesticides may lead to important effects being disregarded and remaining undetected“ to the discussion.

In the original manuscript, we have highlighted a list of gaps in the regulatory risk assessment of pesticides, including lack of or inadequate testing of certain effects (Section “pesticide exposure and health effects”, 1st sentence). Each of these gaps can potentially result in negative health effects a substantial magnitude, but it is naturally very difficult to estimate the magnitude of unknown effects, and the absence of adequate testing is not equal to the presence of effects when substances are released. For the purpose of this review, we therefore focus on known and likely negative effects of OP pesticides regarding neurodevelopment, where ample epidemiological studies and animal experiments exist, that allow for a quantification of this adverse outcome, and where at the same time sufficient evidence has been collected to evaluate causality.

In their discussion the authors raise the important issue of the potential health effects of food processing techniques and correctly suggest that processing may affect the composition and bioavailability of food constituents. They do not however, consider food packaging and food contact chemicals, which may differ between conventional and organic food as identified by a study that found high levels of phthalates in organically produced milk that is most likely to have arisen in either the processing or packaging stage (see Sathyanarayana, S., et al. Unexpected results in a randomized dietary trial to reduce phthalate and bisphenol A exposures (2013) Journal of Exposure Science and Environmental Epidemiology, 1-7).

->Thanks for pointing us to this interesting publication. Indeed, there are no EU rules regarding food packaging, and very few rules regarding food processing, for organic production. That is, we would not expect a systematic influence of the production system on the content of food contaminants from packaging, and we therefore exclude these issues from the present review (in the introduction). Indeed, there are plenty of aspects of food safety which have no conceivable systematic link to the production system (e.g. glass fragments in processed foods). The European Rapid Alert System for Food and Feed, https://webgate.ec.europa.eu/rasff-
list146 alerts related to phthalates in food, but none related to phthalates in organic food (it needs to be kept in mind that the sampling strategy is not systematic).

In this specific paper (Sathyanarayana 2013), we noted that the (potential) use of PVC gloves by catering staff apparently has not been considered a source of DEHP. This could explain the high DEHP concentration in urine from people in intervention arm 1. We have contacted the authors of this study in this regard, who replied that gloves indeed are a likely source of contamination. Also, the design of this study does not allow for a conclusion as to whether organic or conventional foods contain higher DEHP residues.