Author's response to reviews

Title: Estimation of incidence and social cost of colon cancer due to nitrate in drinking water in the EU: a tentative cost-benefit assessment

Authors:

Hans JM van Grinsven (hans.vangrinsven@pbl.nl)
Ari Rabl (ari.rabl@gmail.com)
Theo M de Kok (T.deKok@GRAT.unimaas.nl)
Bruna Grizzetti (bruna.grizzetti@jrc.it)

Version: 2 Date: 7 June 2010

Author's response to reviews: see over
Response to comments by Environmental Health Editorial Team

We have revised the manuscript according to the comments of the three reviewers and the editorial team. In the sequel we respond to all comments and indicate how we adjusted the manuscript. The reviews have certainly improved the manuscript, and also detected some errors.

We have changed the title and have added an additional Table as suggested by reviewer 3. As a result of the suggestions by Reviewer 1 and 3 we also adjusted the formulation of the Conclusions section. All changes are made in ‘tracked changes’.

Both reviewer 1 and 3 suggested some additional and sometimes fairly comprehensive work, which in our view in all cases was not possible because of lack of data or because the added value in our view was small.

Finally we feel that we suffered somewhat the fact that we had two new reviewers who sometimes questioned changes that were made in response to suggestions from the first review (e.g. use of the EFSA reference suggested by the editor after the 1st review; and the suggestion by Reviewer 1 to be less modest about our “tentative results”, while both reviewer 1 and 2 (Dr Dieter) in the 1st review suggested modesty in view of the uncertainties).

- After the title, insert a colon and state the study design. Done
- Please remove the line numbering throughout the manuscript and remove the page numbering in the final version. To facilitate the final check by the editors we have maintained the line and page numbering. Done
- Punctuation should be placed inside quotations e.g. on pages 3, Background section, third sentence, and 5, second the last sentence on the page. Done. We have now quoted the exact and full sentence, including the full stop, for the 3 quotations.
- Footnotes to text should not be used e.g. pages 3 and 9. Removed
- please be consistent and punctuate et al with a period e.g. et al. Done
- In the Methods section remove the lettering of the subheadings. Done: although we do not believe that was helpful when referring to the subsections.
- Numbers 0-9 modifying general items should be spelled out e.g. p. 7 five year age and p. 14 three days. Done
- On page 14 there should be a hyphen between two and thirds e.g. two-thirds. Done
- Please include a list of Abbreviations before the Competing interests section listing the abbreviations and terms in sentence format separating the pairs with semi-colons. Done
- At the end of the Authors’ contributions section insert the sentence, all authors read and approved the final manuscript. Done
- The references in the text should read sequentially but currently jump from 27 (page 12) to 31 (page 15). Delete any references not cited in the text. The jump is caused by using two additional references in Table 3. And indeed we made an error. Done
- The issue numbers in the reference section should be removed. In reference 30, if 8 is a volume number, it needs to be bolded. Done
- All horizontal lines in the tables should be visible. Done
Authors Response to report reviewer 1

Title: Assessing social cost of cancers due to nitrate in drinking water in the EU for the case of colon cancer

Version: 1 Date: 24 March 2010

Reviewer: Martine Marie Bellanger

Reviewer's report:

Overall comments
This a very interesting paper that I would like to see published. However, there are several modifications or complements that, in my opinion, should be made or included before it is published. These are presented below.

Is the question posed by the authors new and well defined?
The question posed by the authors is rather new. As they stated on page 4, “there is no assessment available of social health damage costs resulting from emission of nitrate to drinking water.” I assume that they carried out a literature survey, even though this was not specifically mentioned in their paper. The question addressed is of great interest. There is an increasing need for a valuation approach to enable decision makers to set priorities for interventions and mitigation actions. Taking this into consideration, the authors note (page 4) that different policies have been implemented in the EU countries as well as in the US, while no evaluation of their impact has been carried out.

Response: Thank you for this overall positive evaluation. Indeed we checked the literature and found no studies trying to answer our research question. Pretty et al. 2003, and also Hanley, 1990 partly deal with the same issue but did not assess health costs of nitrate.

Is the question posed by the authors well defined?:
The author’s research question as stated on page 2 of the abstract reads, “the paper addresses the damage cost of nitrates in drinking water and provides some elements for a comparison with the costs of nitrate abatement.” This seems to be slightly different from the sentence on page 4 that states, “Here we focus on health damage and provide only a very rough estimates of the costs of improved water treatment and of reduced fertilizer input.” In addition, this seems to also be different from the title of the paper: “Assessing social cost of cancers due to nitrate in drinking water in the EU for the case of colon cancer.” I’ll come back to the title in question 6 below.

This is a bit misleading: is the paper about social cost of colon cancer, or is it related to a larger issue? This has to be clarified.

I would suggest that the authors re-structure the background question. If possible:

Response: we agree: in the discussion we address the larger issue. This is now clarified in the Background.

To postpone, the § “the present paper addresses …” (page 4), to the end of the “background section,” in order to announce the right question, before the methods used.

Response: we agree: section is moved and rephrased

Could the “unit cost approach” (page 4), be introduced later? This approach does not appear very clear; the formulation has to be revised, and needs improvement for both English writing and economic concepts.

Response: Good suggestion: this section is moved to Methods and adjusted
Also, sentence 3 should be re-formulated: “In fact the question is whether the N-cycle can be changed in such a way, that a welfare improvement is achieved…. Higher mitigation costs and prices of food or energy.

Response: It is not clear to us what the reviewer suggests. The other readers did not seem to have any problem with this sentence.

Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
As mentioned above, some methods have to be improved. Most notably, the economic approach of costs has to be improved by adding one or two main references in economics of environment (e.g. Nick Hanley, see reference below).

Response: Hanley (1990) is included in the Background section, and indeed in part addresses similar questions as in our manuscript. We also refer to Hanley’s findings in the Results.

Page 7: The measurement of Healthy Years of Life (YLLs) and of Years lived with Disability (YLDs) are appropriate. However, I would suggest combining the calculation of Disability Adjusted Life Years (DALYs), which are presently only page 11, and of which the 2 components are YLL & YLD.

Response: we believe that combination of both sections is not an improvement. The subsection on p7 is about quantifying YLL and YLD based on cancer statistics. The subsection on p11 is about economic valuation. The organization of the Methods follows the stepwise scheme in Figure 1; combining both subsections would be confusing.

Page 7: need to be re-written properly: e.g. 3.8 years YLL (Years of Life Lost) = 3.8 YLLs. Response: adjusted, but the ‘s’ can be omitted as YLL is defined as ‘years’.

Page 11: G Loss of life years of monetization) and unit cost - could this become: economic valuation of loss of life years or monetary valuation of loss of life years? I do not really understand what the authors mean by unit cost here? Unit cost of what? Of a year with colon cancer? Or an avoided cost?

Response: Text adjusted. We also moved the paragraph on Unit-cost to the Methods section, as was rightly suggested by this reviewer.

Page 11, bottom, the authors refer to a Value of Life Year (VOLY) of €40,000, estimated by experts from the “ExternE” project on the basis of a contingent valuation method. This finding could be more explicit, as far as they used this value for their calculations on page 12. This § G is a bit confusing, do they authors accept using a “value of statistical life” as economists would do or not? The authors refer to the DG EU commission value of €1 million, and then they return to the € 40,000 per VOLY, with 0.3 VOLYs calculated on the basis of QALY. This is all very unclear.

Response: we have rewritten Section G, now titled Economic valuation of cancers

Finally, additional methods to deal with uncertainty, or with the fact that part of the data is only for Iowa, could have been solved with statistical methods.
Response: We see no simple solution. The essential question to our opinion is if results from DeRoos can be used for EU11. We assume that doubling of colon cancer incidence for exposure for > 10 yrs to drinking water exceeding 5 mg/L NO3-N and above median meat consumption also applies to EU11. And we provide some circumstantial evidence that this doubling may be valid for the EU (Slovakia and Spain). These is no information in our view to use statistics about differences in diet, medical history and life style in the EU and Iowa to modify this assumption. Statistical methods are not very helpful when the dominant uncertainty arises from the interpretation of an insufficient number of epidemiological studies. 

Are the data sound and well controlled?
I have some concerns with the control of certain data, especially those which could be confounding factors in the relationship between colon cancer and nitrate in drinking water.

The authors explain that the dose-response relationship between nitrate in drinking water and cancer is not evident for the total population (Page 8). This is already well known that the relationship is complicated. Nitrate is also ingested in some types of food and medicine. Second, vitamine C and other natural nitrosation inhibitors present in some fruits and vegetables appear to provide some protection against the harmful effects of nitrate ingested with food and water (Braun, 2007). In addition, as the authors explain, there are some type of diets, such as those with high intake of red meat, that seem to further increase the risk of some cancers associated with nitrate intake, such as colon cancer.

Response: we share these views and concerns. With respect to the issues raised by the reviewer we refer to a number of recent papers [3, 4, 5, 6, 10, 11] in four of which two of the authors were involved. There is clearly dissensus and uncertainty which is acknowledged in our manuscript (Table 3 and Discussion)

There are also other diseases such as diarrhea and respiratory illnesses (instead of using word ‘diseases’ twice in one sentence [? Unclear: this does not seem to refer to our manuscript?] that may interact with nitrate concentrations to become risk factors (Braun, 2007). 
As far as I understand, the authors take only the diet factor, but why: shortage of available data?

Response: We are familiar with the UNEP assessment by Braun, 2007. The passage on p18 of this report where this reviewer refers to, in our view, explains that health risks associated with nitrate, e.g. methemoglobinemia, also are related to other diseases like diarrhea (well described in the literature; the present consensus is that methemoglobinemia is not related to nitrate; see also Background p5 ). Our manuscript acknowledges the relevance of other diseases [ref 5 wrt nitrate] and co-factors. We selected colon cancer as this a major disease, and meat consumption as the only co-factor, as this is the only significant co-factor emerging from DeRoos et al.

Then in Equation 3, I do not understand exactly how the author controls for the diet factor. It seems that the population is divided by 2, and the same consumption is assumed in the 11 EU countries as in Iowa. It looks rather limited in terms of assumption. Why don’t they introduce other variables? There are large differences in diet in Europe, for instance.
Response: see earlier response. We divide population by 2, as Iowa data show doubling for “above median meat consumption”; so doubling of risk applies to half of the population. We postulate that relevant co-factors and life style in Iowa in EU11 are comparable. We agree that is a simple assumption, but not a major source of uncertainty in our assessment. Life style and Meat consumption in NW EU and N. America are not very different. Perhaps we could elaborate this somewhat: e.g. meat consumption in Europe and the USA in 2003 were nearly identical (about 90 kg/year; source FAO)

Does the manuscript adhere to the relevant standards for reporting and data deposition? Results account for one page, and discussion & conclusions for 4 pages. This shows that the methods take 8 pages over a total of 18 pages; I was wondering whether this could be better balanced.

Response: That is indeed somewhat unbalanced, but is it bothersome? Central is the assessment of additional incidence and social cost of colon cancer by nitrate. There is some arbitrariness in the organization of any paper. Our results in fact cover two pages as it also includes two tables. The methods section also includes results, that were inferred from the literature (e.g. Figure 2 and 3) to allow application of the different steps of the assessment scheme (Figure 1). Discussion also contains some additional data and assessment.

Page 14: Table 2: very good overall estimations. However, the presentation also needs to be improved. For instance, the sentence: The sum of loss of healthy life years and life expectancy corresponds to 3 days of life of an average consumer. To whom do the authors refer? An average consumer of what? With 3 days of life? And then suddenly, the social cost of this health and life loss appears to be €1 Billion or €2.9 per individual (Average does not seem necessary!!).

Response: Indeed formulations are somewhat sloppy. Our intention was to give the assessment results some practical or political sense. We reworded into: ‘The total loss for these 11 countries is 23000 YLD and 18000 YLL. Although this loss is very modest, it represents a total social cost of 1.0 billion euro per year or 2.9 euro year per person averaged over the entire population (corresponding to three days of additional morbidity and mortality of an average life), and to 150 euro per year for a person exposed to drinking water exceeding 25 mg $\text{NO}_3$/L.’.

One of the recurrent problem in the paper is that the authors do not use always the same concepts. For example, here they use cost of health and life, and on page 8, the healthy years of life. This could be the same here as in table 2? Page 15, they use social cost and unit cost of health loss!!! I have not seen the definition of social cost so far. The authors also use “welfare loss”, e.g. page3, it is social welfare? This has to be clarify, there are economic approaches related to this.

Response: We have taken care that our use of all terms is consistent. Wrt to economic valuation we use general terminology from Cost Benefit Assessments accounting both private costs and benefits (e.g. for a farmer) and public costs and benefits, thus trying to account all effects that influence social welfare (in the broadest sense). By expressing all economic effects in monetary terms CBA is possible, although cost and benefits items can be both market and non market goods. We have adjusted the text of the first section of the Background section, to more systematically introduce CBA terminology.
In table 2, do you make the calculation including the difference in terms of purchaser power between countries?

Response: No we did not; the difference would be totally insignificant in view of the overall uncertainties.

Are the discussion and conclusions well balanced and adequately supported by the data?
The discussion is adequately supported by the results and data. Once again, some of the statement has to be revised: e.g. page 15: they write: “the results for social cost and unit cost of health loss due to nitrate in drinking water should be viewed as tentative values for comparative use against values for other nitrogen pollutants or cost of measures.” This is not the best way to value the authors’ research.

Response: we have slightly rephrased the application potential of our results but think we should be modest about the accuracy of our results on view of the various assumption and uncertainties, in part on suggestion by reviewer 2. The (novel) assessment approach is an equally important feature of this manuscript as are the first results. But still the results allow some provisional new conclusions about cost and benefits of nitrate mitigation.

In the “potential health benefits and mitigation costs,” on page 16, the authors compare the costs of mitigation nitrate interventions (via water media) to the health benefits and estimate a positive net benefits for several countries such as the UK, the Netherlands, Austria & Germany. This is of interest, indeed. My question is why the authors start their paper stating that a CBA would not be possible (page 3 and they have preferred a cost unit approach, page 4). This is rather inconsistent. CBA is clearly recommended on page 17.

Response: We agree that this sounds ambiguous. However, we would not describe the exercise in the discussion as CBA but as comparison of our results with rough estimates of mitigation costs to get a first idea on the net cost or benefit.

Do the title and abstract accurately convey what has been found?
The title has to be revised, once the research question will be addressed more precisely.

Response: we have changed the title

Is the writing acceptable?
The writing has to be revised by an English Native writer, following a more rigorous presentation by the authors themselves.

Some additional references such as Nick Hanley, The economics of nitrate pollution, European Review of Agricultural Economics, 1990, 17(2): 129-151. See also more recent references from N. Hanley, if relevant ;Elisabeth Braun: Reactive nitrogen in the environment: too much or too little of a good thing, United Nations Environment Programme. Division of Technology Industry and Economics? Woods Hole Research Center (Woods Hole, Mass) International Nitrogen Initiative.

Response: we now refer to Hanley, 1990.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests.
Authors response to report of Reviewer 2

Version: 1 Date: 26 March 2010
Reviewer: Hermann H. H Dieter
Reviewer's report:

Minor essential revision:
The summary at the end of p. 15 of what is said in Ref 31 (Schmidt et al., 2008) is not correct. Schmidt et al. describe exclusively the reaction of dimethylsulfamide (DMS) with ozone in some raw waters to give NDMA. They do not describe the reaction of "N-compounds" with disinfectants nor the reaction of pesticides with ozone to give NDMA, nor is their any speculation on such possibilities. At present knowledge, it seems clear, that the formation of NDMA from the ppp-metabolite DMS is a very specific however very relevant example. NDMA as a DBP from chloramines are exhibits a certain significance only if disinfection uses chloramines.
The authors should delete the sentence on lines 21 - 24 on p 15 or reformulate it in a way that it represents their own opinion but not the one of Schmidt et al. (2008)

Response: Reviewer is correct: the overall statement is based on a number of publications in ES&T vol. 42 (2008) on NDMA. We rephrased and used another reference from this ES&T volume (Zhao et al).

“A further illustration of the complexity of the relation between nitrogen in drinking water and human health is the production of the potent carcinogen N-nitrosodimethylamine (NDMA) caused by interaction of disinfection treatment of drinking water sources and environmental concentrations and mixtures of unknown nitrosamine precursors [33].”

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests'
Authors response to report of Reviewer 3

Title: Assessing social cost of cancers due to nitrate in drinking water in the EU for the case of colon cancer
Version: 1 Date: 7 April 2010
Reviewer: Mikael Skou Skou Andersen

Reviewer's report:
In general this is an innovative article addressing an important issue, namely how to arrive at figures for the external costs related to nitrate in drinking water. The article is well written and informative. The article takes epidemiological results for the potential relationship between nitrate and colon cancer as the starting point for an analysis of the social costs related to nitrate in drinking water. While there are few problems with the part of the article that presents and applies monetary valuation for lost life years, the underlying derivation of an exposure-response function for colon cancer as well as the modelling of nitrogen losses is found to be lacking in some respects.

Response: thanks for this positive overall conclusion.

- Major Compulsory Revisions
1. The colon cancer risk derived from the article by De Roos et. al. implies that for the sensitive groups, the number of colon cancer is simply doubled in areas where for drinking water the nitrate threshold is assumed to be exceeded. This somewhat simplistic risk estimate is a problematic starting point in relation to the aim of assigning a damage estimate per kg N used in agriculture (the figure of 0,7 euro per kg N mentioned in the abstract) and hardly allows for a conclusion on the disaggregated damage cost per kg N.

Response: we acknowledge the use of a simple straightforward assumption of risk doubling based on one case-control study. We are not sure what is meant by “hardly allows for a conclusion on the disaggregated damage cost per kg N". Assigning a damage estimate per kg N in agriculture is in fact based on Figure 1, where in spite of the complexity of transport and attenuation processes of N in soils and aquifers, we find a fairly good relation between (modelled) N-leaching from agricultural soils and (observed) nitrate in groundwater in the EU. In the article we further list and acknowledge the considerable uncertainties. We do not agree that our results do not allow for a provisional conclusion about welfare benefits of additional N-fertilizer in the flat range of the crop response curve, or about comparing health impacts from emission of different N-compounds.

2. While the ms. refers to the article by Gulis et. al. and notes reasonable consistency to results for colon cancer, it fails to explore to which extent Gulis could be taken as a more appropriate starting point for deriving an actual exposure-response function for colon cancer in relation to nitrate content in drinking water. More effort should be devoted to justify the choice of De Roos. Are there design flaws in the Gulis study ? Are further epidemiological studies available that would allow the authors to derive an exposure-response function on basis of a broader meta-analysis of available evidence, rather than picking simply one -- incidental ? - study ? If the De Roos study should be regarded as a particular strong or reliable study, the article needs to justify better. Brief reference to the relative merits of case control studies versus cohorte studies in the context of nitrate would be helpful for the readers.
Response: This is a good point. Quantitative (ecological) case-control studies are rare. The excellent paper by Gulis et al. indeed also provides an exposure-response function: 1.66 increase of SIR for nitrate exceeding 20 mg/L nitrate (or 4.5 mg/L nitrate-N) as compared to the reference group. We judged DeRoos to be better suited because (a) it considered dietary and medical risk factors, (b) it distinguishes colon (positive association) and rectal (no association) cancers for which different results were found. For this reason we use Gulis just as circumstantial support for the doubling of risk. Gulis found a 66% increase of incidence for colorectal cancers, while DeRoos found a 50% increase for colon cancer when expressed for the total population. We have added this remark in the text.

3. p. 3: the need for epidemiological studies: are there shortcomings or flaws in the Iowa women's cohort study? (Weyer et al).

Response: In references 4 and 5 some shortcomings (or challenges) are listed. These include uncertainty about medical, drinking water, and dietary history of the studied population; lack of dedicated studies on sensitive sub populations; the need for the development and application of biomarkers for formation and exposure to N-nitroso compounds in molecular epidemiological studies.

4. p. 5, line 6: "nitrate via drinking water is about 4 times smaller than amounts from food" – reference (6) is a magazine – while De Roos states that drinking water can make up as much as 50% in cases of non-compliance with MCL guidelines. Please clarify.

Response: reference 6 is about averages, while DeRoos et al. refer to extremes, the write: “can make up”.

5. p. 6, line 3-4: I found this statement overtly conservative, given that relations to bladder and ovarian cancers were identified in the Iowa cohort study. Again, why is the EFSA magazine referred to, when nitrate is an environmental issue – please check other EU authorities for statements on nitrate and health. The World Bank used the Weyer et al. results for its study “Cost of pollution in China”.

Response: We are not sure which statement is referred to. Lines 3-4 read “….. cohort studies (which provide stronger evidence) find no increased risk with increasing nitrate intake after multivariate adjustment ….”. We assume reference is made to the full quotation from the EFSA journal. The article in the EFSA magazine was brought to our attention by the editor, and in our view contains an excellent and critical review of nitrate in drinking water literature (largely based on a review by FAO/WHO – JECFA).

6. Section D: I found this important section in the article to be extremely brief and uninformative in relation to other sections. A balanced article needs to devote more effort to explore and explain how the results for nitrogen leaching are arrived at, as this is an important area of research in its own. Reference to existing models and approaches and a more reflected choice of approach would need to be included.

Response: Most sections in Methods are of similar length (about one page). Of course depending on the background of the reader, sections may be judged too short or lengthy. Our reason to keep this paragraph short was that our assessment uses a simple straightforward combination of a recently published modelling exercise for EU25 and an accompanying monitoring
dataset for nitrate in groundwater. Reference to other existing models is only relevant here if they are applied on EU scale, which is rare. For calculation procedures we refer to Velthof et al., 2009, but we have added some explanation in the text. We are aware of one other recent European wide model study (CAPRI-DNDC in Leip et al, Biogeosciences 5: 73-94: 2008). One practical reason to use MITERRA, was that the authors had easy access to more detailed model input and output.

7. Section D refers to the concept of ‘mean nitrogen leaching intensity’ with reference to figure 3. Again a dichotomous use of standard exceedence is used, this time it leads to a logarithmic relationship to leaching intensity. No explanation is offered as to how the mean nitrogen leaching intensity was calculated more specifically, which would be required.

Response: see previous response

8. p.9 Why is reference done to private well depth ? Is this because the procedure in section D is used only for the part of exposure related to smaller drinking water supplies ? If so, this needs to be stated explicitly and not left to the guessing of the reader.

Response: yes procedure D is used only for small and private supplies. This is explained in Figure 3 and in the one before last sentence of section D

9. p. 9 “We did not consider temporal trends of nitrate in groundwater”. The MITERRA model by Velthof et. al. is referred to. This model appears to assume that there is a one-to-one relationship between nutrient loss and nutrient leaching – a quite strong assumption underlying the presented calculations and results, which requires some accompanying reflections. What is the possible margin of error introduced here ? Would there be other leaching-models available without such strong assumption and why were their use not preferred? A crucial point to which the authors should add quite some text to explore and justify their approach. Does the MITERRA model for instance allow for appropriate differences in leaching between sandy and loamy soils – if not please clarify the limitations. Is MITERRA stronger on the air pollution aspects of nitrogen than on the leaching side ?

Response: There is no one-to-one relationship, leaching is a variable fraction of the N-surplus, which is also calculated by MITERRA (See response to your point 6). Indeed temporal trends are relevant but on a European scale (e.g. judging from the 4th assessment of Europe’s environment, EEA 2007) trends are not very prominent; between 1992 and 2004 average nitrate concentration in groundwater are only very slowly decreasing. The importance of considering temporal effects to some extent may be deduced from the scatter of Figure 3 of our MS. If the temporal effect would have been dominant, we would not have found a good statistical relation.

10. section E: the statement that data on exceedance of 25 mgNO3/l in large public water supplies are not available for member states other than Netherlands is impossible to accept. The Dutch figure stems from national data, and the authors need to check what data is available at member state level for other member states too. Such data can often be found summarised in english language in SOE-reporting or OECD environmental performance reviews.
Response: We really tried our best. SOE reports by EEA or OECD that we are familiar with report nitrate concentration in groundwater bodies but not in (untreated) drinking water. We are very confident that EEA does not report this kind of data, and OECD uses the same data sources for the EU.

11. Section F. “Implicitly we assume that the association with meat consumption in the EU is the same as in Iowa”. In fact it is also assumed with the risk factor that meat consumption is at the same level throughout the EU as in the US corn belt – so the median threshold needs some correction in the case of Europe. I refer back to my remarks on De Roos versus Gulis and the need for a more informed meta estimate for colon cancer and nitrate, possibly with a more elaborate exposure-response function. Or perhaps the difference between results in Gulis and De Roos can be used to derive a correction factor for Europe if the meat relationship should be regarded as crucial.

Response: Meat consumption in Europe and the USA in 2003 was nearly identical (about 90 kg/year; source FAO). Meta analysis to elaborate exposure-response function is only meaningful when there is fairly large number of comparable studies, which is not the case here.

12. p. 15: line 3-6: in consequence of the above remarks regarding as well the basic risk estimate as well as the leaching calculations the unit damage cost figure is not well consolidated, and the text should signal the difficulties with arriving at a per kg estimate on basis of the data and models employed here. The risk estimate procedure as well as the leaching modelling framework suggests that the figure would be an upper bound value. Inclusion of the figure in the article abstract might invoke misunderstandings without proper underlining of the uncertainties. The same goes for table 2.

Response: we fully acknowledge the large uncertainty of the unit cost per kg of N-leaching, in view of various assumptions. That is why the discussion starts with a section on uncertainty, discussing upper/lower limits of our estimates. From this you can not conclude that our estimate, e.g. the figure 0.7 euro/kgN, is an upper bound. A point not mentioned to amplify this, is that we divide the health cost by the total N-leaching, while you could also argue that only leaching beyond a certain threshold leads to exceedance of 25 mg/l. To some extend this is illustrated in Figure 3, where between leaching of 5-15 kg/ha we see most of the response. So unit damage cost per kg N-leaching are highest in this range.

13. p. 17 line 12-14: “The range of unit health costs for the 11 EU countries found in this paper is 1-7 euro/kgN nitrate leaching would then correspond to a range of 0.1-2 euro/kgN fertilizer input” According to tb. 2 the 1-7 euro is per capita! However, due to big differences in leaching between mineral fertilizer and manure-N table 2 would need to distinguish clearly what sort of N-application reference is made to.

Response: this is indeed was an error. We corrected numbers and adjusted this paragraph accordingly.

14. p. 18 line 1-10: why only reference to fertilizer-N when in line 13 concluding also with respect to manure-N. A small table would be helpful to show the relevant figures now scattered in text.
Response: good suggestion we modified the text and added a small table. We maintained introductory and concluding remarks about fertilizer and manure, but did not include a separate and tentative CBA for nitrate leaching in manure. This is material in prep and press in other publications.

- Minor Essential Revisions

15. p. 11, line 6 refers to figure 1, equation 2 – no such equation is there –

Response: Meant was reference to Methods section H - corrected

(and list of figures + captions missing).

Response: It is present in the submitted MS and the PDF automatically created

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.