

Approaching complexities in health and environment

Proceedings of the HENVINET (Health and Environment
Network) final conference
Brussels, Belgium

Edited by Alena Bartonova, Janna G Koppe, Aleksandra Fucic,
Arno Gutleb, Peter van den Hazel and Hans Keune

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reviewer reports for the articles in this supplement are provided below.

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HENVINET Summary:



Project title: Health and Environment Network

www.henvinet.eu

Background and objectives

The European Union Environment and Health Action Plan EHAP (2004-2010) acknowledges multi-causality in environment and health, and identifies several priority health endpoints. The EHAP is based on the Environment and Health Strategy, which has a long-term vision seeking to address the links between poor health and environmental problems, and “reduce diseases linked to environmental factors”.

Fulfilling this vision requires high level of interdisciplinary knowledge and an ability to communicate within and between science and the decision making sphere. To contribute to this vision, the Health and Environment Network HENVINET aimed to create a permanent network of professionals, in order to provide policy relevant scientific advice, and to tackle communication gaps in environment and health.

Addressing transdisciplinarity for policy

The project had the ambition to synthesize scientific information available on a number of topics of high relevance to policy makers in environment and health, with the aim to support the EHAP 2004-2010. Initially, we planned to carry out separate reviews of the knowledge base, to evaluate the available knowledge and to provide the advice as of scientific publications. Soon, the consortium was forced to rethink the literature review and publication strategy for knowledge evaluation. To be able to communicate across the multi-partner and multidisciplinary expert group, the consortium decided to adopt a common structuring framework, the WHO DPSEE¹⁾. This framework was used consistently throughout all the project elements. We had also to review existing knowledge evaluation criteria, to adjust them for our purposes, and to develop a web-based version of expert elicitation. This has evolved further into defining communication needs and adopting social media to address them.

The methods we used, including the expert elicitation, the application of the calibrated confidence levels as a scale for evaluation of knowledge, and the problem solving approach, were all challenging for the consortium as well as for external experts. These approaches were outside the environment and health scientific practices normally employed by the participants. Thus, we extended the scope of the work from solely addressing the scientific issues, to also include the more problem solving policy perspective and thus arising communication needs. Therefore we could also address the issues of what policy action the experts consider justifiable.

This process of accepting the trans-disciplinarity and addressing it that the consortium went through illustrates the type of challenge to be met in order to fulfil the scientist’s role as a responsible actor in the society.

¹⁾ Drivers-Pressures-State-Exposure-Effect-Action, see <http://www.who.int/mediacentre/events/IndicatorsChapter7.pdf>, last downloaded October 2010

Knowledge evaluation

HENVINET has developed a knowledge evaluation method and applied it to examples taken from four groups of health endpoints: asthma and allergies, cancer, neurodevelopmental disorders, and endocrine disruptors. The evaluation methodology has three main steps. First, questions were formulated, and based upon scientific review, translated into a visual schematic framework using causal chain diagram. A web-based questionnaire was developed to engage external experts to assess the diagrams completeness and accuracy, and the state of knowledge

in each element and link. In the second step, the results of the first step are summarized and submitted for external expert discussion with the aim to identify expert agreements and disagreements, and to provide a list of prioritized actions for policymakers. In the final step, the results are submitted to decision-makers for feedback on the process and results.

The online expert evaluation was performed for three types of cases: a policy question, a risk assessment paradigm, and question of environmental determinants of

disease. The policy questions evaluated were “what are the effects of climate change on respiratory health”, and “what is the role of traffic pollution in exacerbation and onset of asthma and allergies”. Knowledge within the risk assessment paradigm was evaluated for phthalates, chlorpyrifos, and the brominated flame retardants DecaBDE and HBCD. Environmental determinants of disease were assessed for specific types of cancer. An additional questionnaire has been constructed for the area of nanoparticles with the aim to prepare for expert assessment of knowledge across the whole DPSEEA chain.

An example of how issues can be visualised is given in Figure 1 that provides a general causal diagram for breast cancer related to selected persistent organic pollutants. The experts were to evaluate to what extent these issues can be linked together.

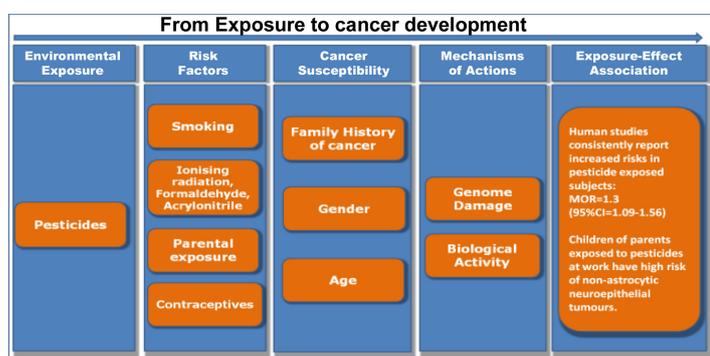


Figure 1. Causal diagram illustrating the potential link between brain cancer and environmental exposure to pesticides.

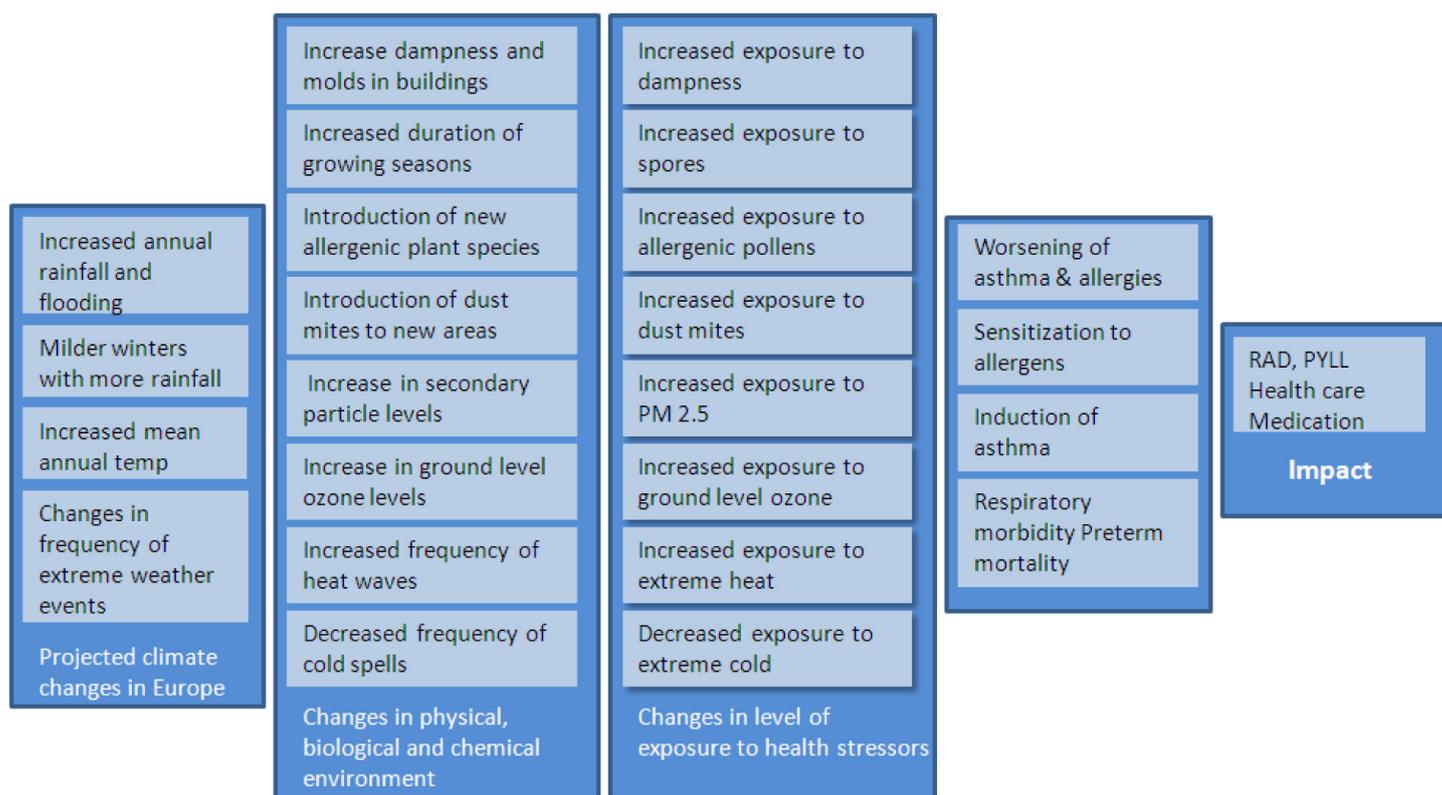


Figure 2. Causal diagram on climate change and respiratory diseases developed as a basis for knowledge evaluation.

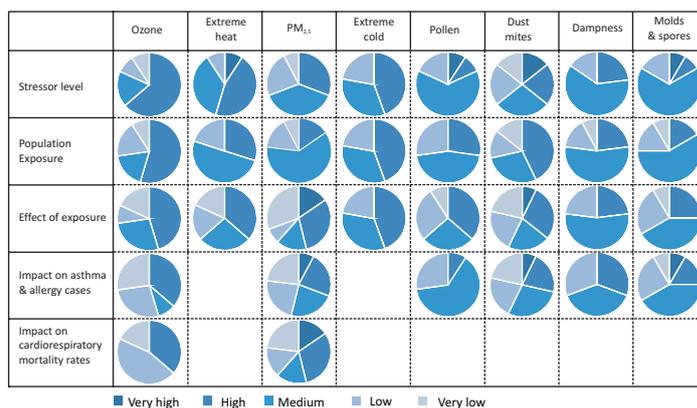


Figure 3. Evaluation results for the diagram on climate change and respiratory diseases: Confidence in the ability to predict individual elements of the diagram (lines) for the selected stressors (columns).

Another approach was taken when addressing a question of climate change and respiratory disease. Eight climate-change related exposures and four kinds of effects related to respiratory health were identified and then assessed (Figure 2). The results show that despite having been studied intensively, exposure to particulate matter is still considered the most difficult to assess (Figure 3).

Meta databases of decision support tools and of environmental health projects

In HENVINET we defined decision support tools (DSTs) as “any tool based on E&H Knowledge that can be used for making decisions for reducing the negative health effects of the environment, from the daily operational level to the long term policy making perspective”.

Information gathering about DSTs aimed at characterizing and evaluating a variety of different ‘tools’ that can be used at various levels (international, national, local) and by various stakeholders (politicians, engineers, planners, doctors, environmental scientists). The DSTs are described using a number of attributes:

- DST category, e.g., guideline, indicator, software model),
- thematic area within the DPSEEA framework, e.g., type of and specific stressor, environmental matrix, exposure route, health end point,
- decision making area and level,
- user friendliness, robustness, and availability of information on uncertainty.

Each of these attributes has multiple descriptive categories, based both on a number of existing systems for knowledge categorisation and subject lists, and on own lists.

Information about DSTs is provided in a searchable meta-database, publicly accessible at <http://www.henvinet.eu>. At the end of the project, the database contains over 60 quality-controlled entries, and new entries can be added by any registered external user.

The most common type of DST is a software model with over 50% of entries in this category. Databases, guidelines and methodologies are less frequent. Indicators and handbooks are the least common category. Regarding environmental stressors, Figure 4 shows that the majority of DSTs are applicable for more than one stressor.

A similar but less complex database has been created for E&H projects. Searches are available for free text, and for project type and funding source categories.

The web-based searchable metadatabases are accessible through the HENVINET web pages and the networking portal.

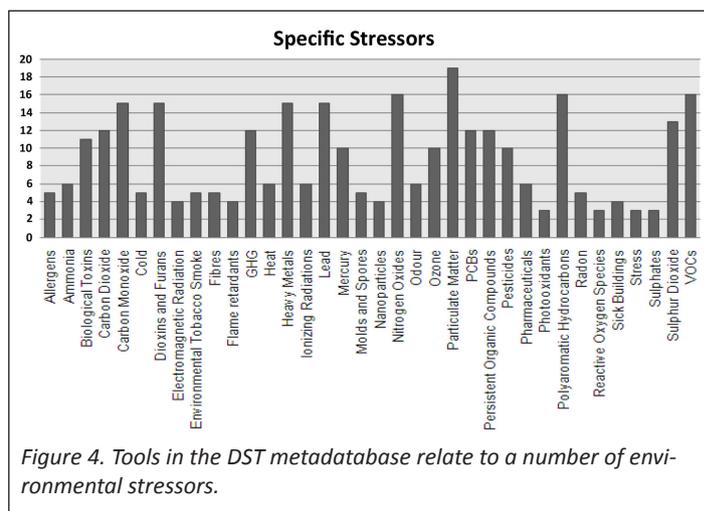
Networking the health and environment community

Stimulating and facilitating interaction between policymakers, scientists and other stakeholders from civil society and industry is not an easy task. HENVINET had the ambition to establish an integrated social network and networking facilities for multiple stakeholders, to ease communication between the different actors involved in decision-making.

A diversity of methods was employed:

- face-to-face consortium meetings to create common communication basis for the multidiscipline and multi-stakeholder consortium,
- multiple knowledge evaluations involving remote evaluations followed by face-to-face meetings,
- a role-play activity, and
- stakeholder workshop.

As a main outcome, the HENVINET online networking portal is established on <http://www.henvinet.eu>. Its main aim is to provide a tool for communication between and within



environmental health communities to create a permanent network between researchers, decision makers and other interested stakeholders. The main functionalities are a personal profile page registration and search for experts, participation in groups and forums and in general, sharing of information through discussions and searches of own content. The portal also provides access to the project results.

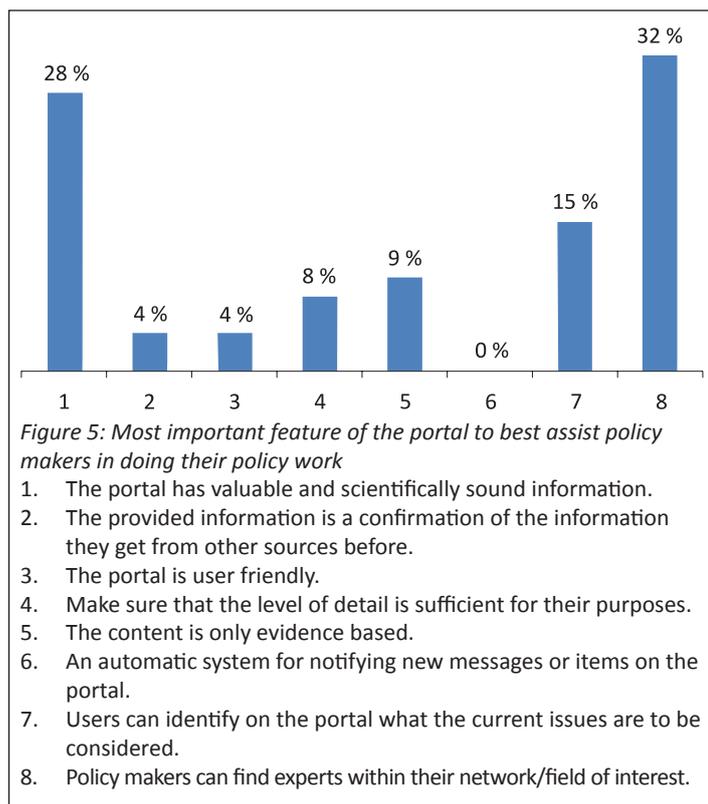
This web-based “virtual network” is able to keep its relevant health and environment content current through continuous member contributions. Members can engage to share or gain expertise, views and information. It is possible to search for and pinpoint scientific expertise, and to communicate and discuss concerns and specific topics with experts worldwide, with the aim to shape the agenda of the Health and Environment community.

Networks such as HENVINET are created not only for the benefit of the network being established, but also to be used as learning tools for future network building. Apart from facilities such as a networking portal and organizing other networking activities, the importance of specialized intermediaries or moderators should not be underestimated for enabling effective communication between different groups.

Feedback on the social networking portal

We have asked our colleagues for their feedback HENVINET, as a survey of over 50 participants at the final workshop. Most participants were researchers (44%), and stakeholders developing decision support activities and policies (25%) or providing public information on E&H (17%). Asked for the portal’s most important feature to assist policy makers in their work, 32% of the participants assume that policy makers could use the portal to find experts within their field to provide them with scientific sound information (28%). 15% consider as most important feature the fact that the portal helps the users to identify current issues on E&H (Figure 5).

Almost a third of the participants (28%) think that the foremost reason for a policy maker to become member of the HENVINET portal will be the fact that he/she can interact with a well-known scientist directly and receives infor-

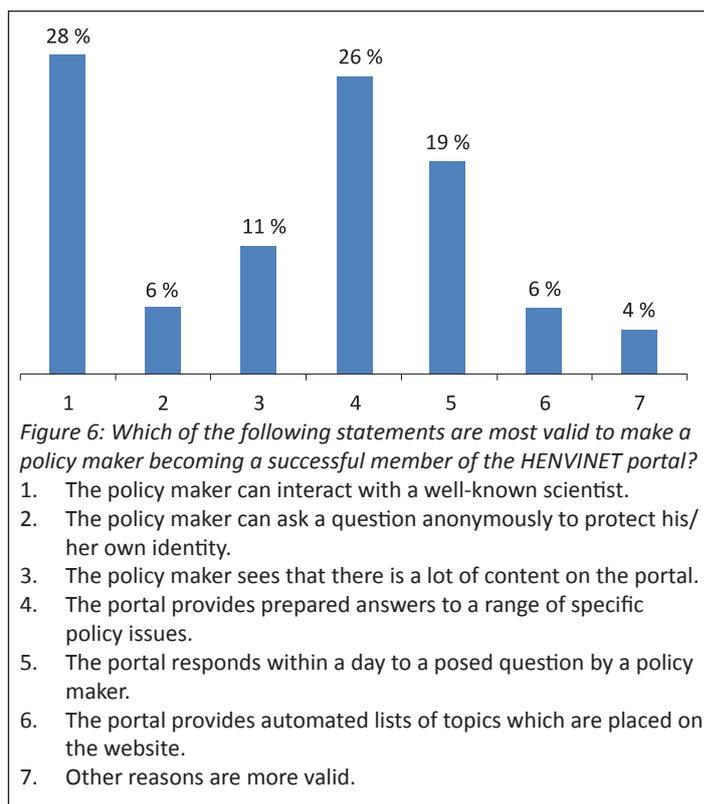


mation/answers to a range of specific policy issues (26%) (Figure 6).

Participants also indicated that they would be willing to invest time into the HENVINET portal. However, the foremost precondition to make the portal a suitable communication instrument is that it must provide adequate scientific information prepared in a way that can be used easily by policy makers. To be used to its full potential, active content development and recruitment are needed.

Impact of the project

Twenty-five organizations from Europe and 5 outside joined in this 3,5-year effort to create a permanent network in



Health and Environment, including environmental research actors, public health actors, veterinary medicine, medical practitioners and local administrations. Over 100 scientists outside the consortium and a number of policymakers have actively been involved in the project activities. Our brand name HENVINET is recognised in Europe. With over 350 users of our social networking portal, it is a number that is significant by any measures.

Another impact of the project over time is the experience that for successful science-policy interface, scientists need not only their scientific knowledge, but also understanding and appropriate tools that would enable them to communicate this knowledge to the decision-makers.

Contractors involved

1. Norwegian Institute for Air Research (NILU), NO
2. National Veterinary Institute, NO
3. The Ecobaby Foundation, NL
4. United Bristol Healthcare NHS Trust, UK
5. Public Health Services Gelderland Midden, NL
6. Central Science Laboratory, UK
7. Slovak Medical University, SK
8. Institute of Food Bioresources (IBA), RO
9. Italian National Agency for New Technologies, Energy and the Environment (ENEA), IT
10. World Health Organization (WHO) – European Centre for Environment and Health, INO
11. University of Hertfordshire, UK
12. Wageningen University, NL
13. University of Oslo, NO
14. Netherlands Organisation for Applied Scientific Research (TNO), NL
15. Finnish Meteorological Institute (FMI), FI
16. Directorate General Joint Research Centre (JRC), INO
17. Piemonte Region, IT
18. Institute for Medical Research and Occupational Health, CR
19. Umeå University, SE
20. Slovak Technical University, SK
21. Norwegian School of Veterinary Science (NVH), NO
22. Stockholm University, SE
23. University of Southern Denmark, DK
24. National Centre for Scientific Research “Demokritos”, GR
25. Argentine Association of Doctors for the Environment (AAMMA), AR
26. Peking University School of Public Health, CN
27. Integral University, IN
28. eThekweni Municipality, ZA
29. National Institute for Public Health of Mexico (INSP), MX
30. National Institute of Health (ISS), IT
31. National Cancer Research Institute, Genoa IT
32. University of Antwerp, BE

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S2
Title	From review to facebook: inter-disciplinarity and empowerment in health and environment
Author(s)	Alena Bartonova
Referee's name	Hans Keune

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: good overview paper !

Major compulsory revisions: none

Minor essential revisions:

First, it strikes me that you mainly (if not only) mention communication when you discuss interdisciplinarity, and not collaboration or some word of that nature. To my understanding interdisciplinarity is about creating new knowledge with the input and interplay of a diversity of disciplines, as if their diversity of expertise more or less fuses to create something new, different than merely adding the disciplinary parts, as is being the idea behind multidisciplinary. To me collaboration comes closer to e.g. the work being done in WP1, especially with the workshops, and to the Henvinet approach in general. Of course communication is an important part of this, but not the only. In the slip stream of this focus on communication, it seems that you mainly focus on informing policy makers and society, and not so much at solving environmental health problems, as if problem knowledge will automatically result in problem solving, and as if scientists only have the task or responsibility to inform and warn, and nothing more. Maybe the latter is your opinion (not necessarily mine), but you could be clearer on this I guess.

Second it strikes me that you specifically and only use the word interdisciplinarity and not (also) transdisciplinarity. I think that part of the Henvinet work (be it communication, networking, collaboration, whatever) was transdisciplinary of nature, as it involved not only a diversity of scientific experts, but also non-scientific experts such as policy representatives, stakeholder representatives, or hybrid expertss such as e.g. Gavin Ten Tuscher and Janna Koppe. Transdisciplinarity is of the utmost importance especially when more than merely a purely scientific endeavor is aimed for, e.g. if we really want to solve problems and take knowledge a step further to concrete action. I guess that e.g. the Climate change – Cities workshop was an example of this, but also the network in general and also the project.

Third: some language issues could be dealt with, some words missing here and there.

Discretionary revisions: none

Continue on a separate sheet if necessary

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S2
Title	From review to social media like facebook: inter-disciplinarity and empowerment in health and environment
Author(s)	Alena Bartonova
Referee's name	Dorota Jarosinska

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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

The manuscript presents the origins, concept, and objectives of the FP6 supported coordination action "Health and Environment Network" HENVINET. This is an introductory paper that provides an overview of the project and points out several specific outputs of HENVINET, discussed in separate papers. Interdisciplinary nature of HENVINET is highlighted, and several aspects of 'interdisciplinarity' in environmental health are introduced. The manuscript would benefit from a more in depth reflection on which aspects of interdisciplinary work within HENVINET posed major challenges, and which turned out to be a success.

A role of social networking to facilitate interdisciplinary work is discussed; however, as rightly stated, sustainability of such a network is a challenge. However, this aspect is not analysed in more depth.

The writing of the manuscript is acceptable. The title of the manuscript seems to be much broader than actual content of the manuscript.

Major compulsory revisions:

Minor essential revisions:

The author may consider revising a title of the manuscript to reflect better its nature. The manuscript needs final check of references, and will benefit from a final text editing.

Fig.1 - please provide explanation for acronyms used (DPSEEA, ICT).

Fig 2 –it is recommended to revise this figure and propose another way of presentation

Discretionary revisions:

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S2
Title	From review to Facebook:inter:disciplinarity and empowerment in health and environment
Author(s)	Alena Bartonova
Referee's name	Jann Koppe

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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: This is an excellent review and also overview of the Henvinet project and refers in the same time to the content of the supplement.

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions: Some typo's and little changes

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S3
Title	We're only in it for the knowledge? A problem solving turn in environment and health expert elicitation
Author(s)	Keune et al
Referee's name	Janna Koppe

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3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
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7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

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Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: article can be accepted

Major compulsory revisions:

Minor essential revisions: I can accept now after my minor corrections.

Discretionary revisions:

Continue on a separate sheet if necessary

Dear Hans Keune:

Yes I agree now with this version, just the following: on page 2 in the abstract I don't understand what you mean with complimentary focus, focus on what? I now added a clarification. An anecdote of the Delphi method, when this was published in the Lancet out of their evaluations it became clear that alcohol is doing much more harm in society than heroin. And that is true, a baby with fetal alcohol syndrome is much more damaged than a baby of an heroin addicted mother. Well and you all know the policies of today in this field.

You are right that you cannot change "Knoll's words. In my perhaps biased opinion I think that Knoll's group has a little bit too much "Jesus Christ on their shoulders". What a nice expression J What exactly do you mean by it?

Yes, you are right, indeed a choice is given to use the word background or introduction.

Page 8 you speak of an unbearable workload, might others not think we were lazy? I now added a clarification.

Page 11: I think you have to refer to Aleksandra's and Franco Merlo's paper also published in the supplement (I'd be happy to, also the other topical papers, can you send me the references you have?); in the instructions for authors they mention how to do that, by the way, everybody, who is an author should be given their email addresses immediately after their institutions. Added now.

The framing for medical research I have proposed to use, I have no reference for you, in Franco Merlo's paper he is mentioning it as a pyramid (I'd be happy to consider this as one example framework for the field of E & H (there are more, but that's not the focus of the paper), but first would like to look into it in order to judge how we best consider this to be relevant; can you send it to me?). Somewhat of my frame is adapted by him. It was described by Dr. van Everdingen in his column without a reference, of the monthly paper published by our governmental research institute for prevention, where Mackenbach from Rotterdam is now the chairman, also a social science guy. It is common knowledge and I learned about it when I was a member of the medical ethical committee for research. But you might mention Franco Merlo's paper for that. In risk assessment animal studies are used in principle, because the probability of doing harm to humans must be prevented, so they don't use this frame and keep to the lowest one nr.5: animal studies. The studies in humans in most risk assessments are very scarce by that reason. And there is also a policy of not doing studies in human beings, an example is f.i. the study to effects of dioxins, because of political reasons a follow-up of an excellent cohort in Rotterdam and Groningen is not done, a "missed observation" in my opinion in the pyramid or frame of what is wrong in medical science this is the worst.

About the "Holy Grail", what I miss is the category "clinical medical experts". Can you please be more specific: where and with respect to which issue specifically in relation to the paper? I think you should make a sentence about them. Their opinion can be 100 % different from the opinion epidemiologists have. I have two examples of that and that is important, because an epidemiological study is immediately disqualified, if a clinical medical expert in the field is discussing their interpretation by telling the interpretation is nonsense and comes up with good arguments.

Anyhow I agree with this paper as it is, if you take care of these little remarks.

Janna

The answer of the author was:

Dear Janna,

Thank you for your extensive review of the paper; as I did not receive any other specific review, I reply here to your suggestions. In general I think two issues are important.

One is the misunderstanding that this paper is about the topic specific outcomes of the topic evaluations. These though will be dealt with in individual topic papers. This paper is about the method and evaluation of the method. As such the material of the evaluation section of the method is social scientific data.

Second, several issues appeared to be unclear, even though many of them are in fact being dealt with in the paper. I have clarified this in your review document in attachment.

Are you comfortable with this?

Also attached a revised version. Can all of the co-authors please have a look?

Sonja, can you please forward this to the co-authors who are not in this mail? I especially ask this as Aleksandra after reading the paper did not feel comfortable with being included as co-author.

Thank you, Hans

Hans Keune

My answer see above sent on August 28 2010.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S3
Title	We're only in it for the knowledge? A problem solving turn in environment and health expert elicitation
Author(s)	Keune et al
Referee's name	Janna Koppe

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

Review for the authors: re: manuscript: We're only in it for the knowledge? A problem solving turn in environment and health expert elicitation. Authors: Hans Keune cs.

This is a lot of work to summarize what happened in WP1 and the turn that was made by Martin KvK to get a frame how to come to solutions with available knowledge. So I respect very much all the work done to come to this article.

My main problem is the structure of the abstract and the article. I think it needs reshuffling.

The heading: Background, both in the abstract and the article, must be changed in "Introduction".

May I make the following suggestions?:

Abstract:

The lines starting with "The topics investigated etc until the end of the alinea are part of the method. In the introduction I should mention the 5 methods used in medical research in general to medicaments and other interventions or toxicants. The Holy grail as you mention it is the "Randomized controlled trial", so that is nr 1. Second best is a prospective cohort study, nr 2. Third: a case study. Fourth: expert elicitation. Fifth: animal studies . Because pollutants are addressed the first ideal method of medical research the randomized controlled trial is not possible for ethical reasons. The second is a possibility , but means a long term research of many years and the third method is depending on a disaster that takes place. So for our purpose expert elicitation is the best if a rather fast method , how to come to a decision is what is necessary. And then at the end of the introduction you tell what the paper brings. For instance: "This paper is mentioned to describe expert elicitation as a method to evaluate knowledge and make decisions or formulate policies for problems that arise by environmental pollutants that might influencing health ."

Methods:

Under this heading I suggest that is described:

Reviews were made, etc and the following topics were investigated etc so what is said now under the background. Then workshops were organized, how many?? Are not both questionnaires qualitative? And that policy briefs were made?

Results:

Here you have to give the results: f.i.the number of reviews and if they are published or submitted and then the results of the workshops, how many people were in the workshop and what was the percentage of a certain opinion.

What is now said under results is better placed under a heading "discussion".

Conclusion:

The question of the Holy Grail and that there is no best method etc I should delete. That is clear from the fact that this method is nr 4 in the row of how to do medical research.

Re the Article itself:

I should start with the heading : Introduction:

I don't see why the specific headings are used in the introduction or as is now named background , unless you say first, that you give a historically overview of what happened during the project: That indeed started with :The ambition of knowledge evaluation, and then I agree what is written on page 7 and 8 and part of 9. Then you switch to policy interpretation, but that was later, first came Martin's idea for expert elicitation, and then you can come with the material now on page 5 and 6. By the way I don't understand what Knol means with "to inform policies", must that be politicians?? I disagree with her idea that expert elicitation happens before conclusive scientific evidence becomes available, because she doesn't define what conclusive scientific evidence is. You may question if conclusive scientific evidence is ever available. In reality decisions made after expert elicitation are continuously under scrutiny and criticism when new knowledge becomes available. And then the two other phases you can mention. The policy interpretation and the third phase, the policy briefs.

And after that at the end of the introduction you summarize why you make this paper:

For instance: In this paper a method is described how to do expert elicitation, being the best method available for our purpose to come to knowledge evaluation and translate that into policies. Experiences with this method are described.

And then under methods:

Describe the reviews how they were made and why these items (Deca, HBCD, Phthalates, climate change, nanoparticles, chlorpyrifos and cancer) were addressed.

And how the questionnaires were made.

And then under results:

The outcome of the questionnaires and workshops.

And then a new heading discussion, where you describe the feelings, now so very well described on page 11 to 26. You can also make a heading: Appendix: and put in there what everybody has said. To me that part:

Evaluation by experts consulted by Henvinet was the best part of the article, because with so many remarks I could identify myself.

And after the discussion a conclusion. In the conclusion the method must be mentioned in perspective with medical research in general and maybe you can say that it is the best method in the circumstances given.

Janna Koppe Aug.12th 2010.

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S3
Title	We're only in it for the knowledge? A problem solving turn in environment and health expert elicitation.
Author(s)	Hans Keune, Arno C Gutleb, Karin E Zimmer, Solveig Ravnum, Aileen Yang, Alena Bartonova, Martin Kraye von Krauss, Erik Ropstad, Gunnar S. Eriksen, Margret Saunders, and Bertil Forsberg
Referee's name	Peter van den Hazel

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: Good article, suitable for those who like to read about formulas

Major compulsory revisions:

Minor essential revisions:

The three phases in the methods part seem to come up suddenly without any prior explanation; this could be made more clear in the part of expert elicitation

Discretionary revisions:

in the text some questions raised;
redraft of abstract according to methods, results, conclusions; for clearer abstract

Referee’s comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S4
Title	An expert assessment on climate change and health – With a European focus on lungs and allergies
Author(s)	Bertil Forsberg et al
Referee’s name	Peter van den Hazel

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: Sometimes some sentences are long and get tangled up. The idea of causal diagram should be explained, as it is part of the goal of the study. It is not always clear if the impact on the stressors is judged or the health effects within the causal chain. It seems two kinds of confidence judgements are running alongside. Maybe this can be made more clear. The time frame on which the judgements are based are not clearly stated. This will influence the confidence levels considerably. Can the discussion refer to some work done on the future expected impacts by other studies? In what matter are there similar conclusions?

Major compulsory revisions:

Minor essential revisions:
In the text minor questions and grammar suggestions.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S4
Title	An expert assessment on climate change and health-With an European focus on lungs and allergies
Author(s)	Bertil Forsberg et al
Referee's name	Janna Koppe

When assessing the work, please consider the following points, where applicable:

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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: this is a good article

Major compulsory revisions:

Minor essential revisions: I only think that in the title it must be “an European and not a” that is all I could find in the field of typo’s, further on it looks fine and can be accepted.

Discretionary revisions:

Good article, easy to read, well written, can be accepted without revision, only one typo in the title.

Referee’s comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S5
Title	Chlorpyrifos and neurodevelopmental effects: a literature review and expert elicitation on research and policy
Author(s)	Saunders et al
Referee’s name	Gutleb AC

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:
A well-written manuscript that need only some editing (and answering questions raised by other reviewers). I have made comments directly into the manuscript.

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions:
 All typing errors I found you will find in the manuscript that the editor will provide.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S5
Title	Chlorpyrifos and neurodevelopmental effects: a literature review and expert elicitation on research and policy
Author(s)	Saunders et al
Referee's name	Aleksandra Fucic

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

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- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: This is excellent manuscript which gives current knowledge on CPF and inform about possible ways to reduce exposure of humans especially of children. Interpretation of experts' reports on the topic is given in the most objective way and related with possible changes in legislation.

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions:

The problem of storage of produced CPF after being banned is significant and simultaneously reliable technology of destroying of this chemical has to be available in order to avoid leakage in few decades. This could be mentioned in discussion.

Continue on a separate sheet if necessary

Policy relevant results from an expert elicitation on the health risks of phthalates by Zimmer et al

Assessment by Espen Mariussen

The manuscript presents a tool to evaluate health issues of chemicals by experts in the field, which can be convenient for policy makers and stakeholders. A major challenge for policy makers today is to get updated scientific information about health effects of chemicals. Such information is important to get in order to do reliable assessments of use and production and for public information. The method presented aims to identify knowledge gaps and scientific confidence in current knowledge based on a set of criteria relevant for health issues. This work is an important contribution to develop such improved tools, but I have some comments about the manuscript that should be considered by the authors in a revised version.

First, and perhaps most important, as I read the manuscript it is a presentation of a tool for policy makers to assess health effects of chemicals. The manuscript is also an assessment of phthalates and I feel that you try to tell two stories in one and, therefore, loose focus. You should be more clearly on whether you are testing a method for assessment of chemicals, or if you do an assessment on a chemical based on a method.

In the Background section the aim and goal of the study is presented very early in the text. It should be moved to the end. The structure of the Background should, therefore, be changed.

You present a tool for policy makers, but do not discuss the alternatives in light of your method. What is current procedure for stakeholders? Pros and cons? Do your method represents a more quantitative and objective approach to the challenge?

In the Discussion section you primarily discuss the expert opinion, but not the response of the decision makers, which, I presume, are the user of the tool. How can you convince decision makers that this is a preferred method (you got very few respondents)?

In the method section you (page 9, line 1) you introduce a workshop. Information about that workshop comes later, this is confusing. What was discussed on the workshop, the method or the assessment of phthalates? This comment can be linked to the abovementioned comment, whether you are testing a method for assessment, or if you do an assessment based on a method. You should go carefully through the manuscript and remove unnecessary information. Is, for example, a table on the workshop agenda relevant for the manuscript? Is it relevant for the manuscript that "four people from HENVINET were keeping the minutes"? Is it possible to reduce the numbers of sections in the Methods? The sections in the Results should, in larger extent, reflect the sections in the Methods.

In order to access the additional files you have to register on HENVINET webpage. These files should be made more easily available, for example as downloadable files on the journal web page.

There are some grammatical errors in the text that should be corrected. Some sentences are long and complicated.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S6
Title	Policy relevant results from an expert elicitation on the health risks of phthalates
Author(s)	Karin Zimmer et al
Referee's name	Aleksandra Fucic

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

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- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

Manuscript "Policy relevant results from an expert elicitation on the health risks of phthalates" by Zimmer et al. is well structured and gives good overview of model used for evaluation of relevant issues on health risks after exposure to phthalates. Manuscript gives detailed approach on selection of experts and structure of questionnaire in order to extract the most relevant conclusions on this topic for improvement of legislation. Title, abstract and reference are well prepared and informative.

Major compulsory revisions:

Listed detailed comments are suggested in order to improve the manuscript:

1. Manuscript is too long as it goes in too many details which are not relevant for readers who may use the described model in future
2. Page 5. Chapter which starts with "Within work... until the problem solving perspective." Should be deleted as it is not relevant
3. Page 7. Delete the first sentence in the chapter Methods as it is not appropriate to cite submitted manuscript.
4. In the same chapter delete sentence "Every diagram element box.....until the could be redone starting from the beginning. Should be deleted as it goes to irrelevant details.
5. In the next sentence HENVINET should be written in capital letters.
6. page 10. Chapter "Workshop reports" should be deleted as it is irrelevant
7. page 11. Write what means "NOAEL" (No observed adverse effect level)
8. page 13 it is too long
9. page 14. The second chapter of "Expert-opinion of the elicitation and the approach used" should be deleted
10. References are in different colours! Please correct fonts and colours.
11. page 26. Figures are missing
12. Table 2 workshop agenda, delete it as it is irrelevant
13. page 31 Additional files should be deleted or such supplement should be reorganized.

Response to reviewers' comments

Reviewer 1

Major compulsory revisions

Listed detailed comments are suggested in order to improve the manuscript:

1. Manuscript is too long as it goes in too many details which are not relevant for readers who may use the described model in future
2. Page 5. Chapter which starts with "Within work... until the problem solving perspective." Should be deleted as it is not relevant
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10. References are in different colours! Please correct fonts and colours.
11. page 26. Figures are missing
12. Table 2 workshop agenda, delete it as it is irrelevant
13. page 31 Additional files should be deleted or such supplement should be reorganized.

Our response:

1. The manuscript is now revised according to the later comments which implied deletion of several paragraphs
2. Ok, deleted
3. According to the guide for authors, manuscript submitted to the same supplement could be cited and put on the reference list in red (for the journal to update to the correct details in the publishing process).

4. Ok, deleted

5. Ok, now in capital letters

6. Ok, deleted

7. OK, now: "NOAEL" (No observable adverse effect level)

8. Yes, this is a long paragraph,. However, since many of the answers to questionnaire 2 are qualitative, it needs some space to be described. By going thoroughly through, it was confirmed that the whole paragraph sums up the answers of this questionnaire in a simple manner without superfluous text. It is therefore not possible to make a good shorter version of this paragraph without skipping results.

9. This paragraph is also difficult to delete. The reason is that the experts wanted this to be part of the results, which it really is. This was an important part of the workshop. The plan was to describe this in phthalate paper but not the paper on the brominated flame retardants. Some experts were sceptical about the whole project. They wanted a discussion of the usefulness of the method and whether it was appropriate to use it. Of course it is also discussed in the discussion, but there it is more on a general level, and seen from an overall perspective including our own experiences.

10. The reason can be found in the guide for authors where they say that manuscripts submitted to the same supplement may be cited and marked in red in the reference list.

11. As the figures where to be submitted in pdf-format they where given separately.

12. OK, deleted

13. Additional files, which the journal calls it, should be given, according to instructions for authors, as such a list at the end of the manuscript-file. The additional files themselves are given in separate files.

Reviewer 2 (blue our response)

First, and perhaps most important, as I read the manuscript it is a presentation of a tool for policy makers to assess health effects of chemicals. The manuscript is also an assessment of phthalates and I feel that you try to tell two stories in one and, therefore, loose focus. You should be more clearly on whether you are testing a method for assessment of chemicals, or if you do an assessment on a chemical based on a method.

The two stories are still told in the revised manuscript. However, we have tried to make clearer that to develop the tool, it was necessary to use a real issue. Besides, the aim has been slightly changed to 1) use the developed tool to assess health risk of phthalates and 2) evaluate the tool.

In the Background section the aim and goal of the study is presented very early in the text. It should be moved to the end. The structure of the Background should, therefore, be changed.

This is now changed

You present a tool for policy makers, but do not discuss the alternatives in light of your method. What is current procedure for stakeholders? Pros and cons? Do your method represents a more quantitative and objective approach to the challenge?

Risk assessment as an alternative was already mentioned. It is now more thoroughly discussed in a new paragraph of the discussion.

In the Discussion section you primarily discuss the expert opinion, but not the response of the decision makers, which, I presume, are the user of the tool. How can you convince decision makers that this is a preferred method (you got very few respondents)?

The discussion and the conclusion should be quite convincing. Probable reasons for the low response are now discussed.

In the method section you (page 9, line 1) you introduce a workshop. Information about that workshop comes later, this is confusing. What was discussed on the workshop, the method or the assessment of phthalates? This comment can be linked to the abovementioned comment, whether you are testing a method for assessment, or if you do an assessment based on a method.

Sections are now combined and reorganized. The workshop is now carefully introduced.

You should go carefully through the manuscript and remove unnecessary information. Is, for example, a table on the workshop agenda relevant for the manuscript? Is it relevant for the manuscript that "four people from HENVINET were keeping the minutes"? Is it possible to reduce the numbers of sections in the Methods? The sections in the Results should, in larger extent, reflect the sections in the Methods.

Some parts of the text have been removed, sections have been combined and reorganized and the sections of the Results now better reflect the Methods sections

In order to access the additional files you have to register on HENVINET webpage. These files should be made more easily available, for example as downloadable files on the journal web page.

This is not true. The additional files were submitted together with the manuscript and will be published in the special issue as supplementary data.

There are some grammatical errors in the text that should be corrected. Some sentences are long and complicated.

A native English speaker has now gone through the text and corrected.

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S7
Title	Policy relevant results from an expert elicitation on the human health risks of decabromo-diphenyl ether (decaBDE) and hexabromocyclododecane (HBCD)
Author(s)	Ravnum et al
Referee's name	09.03.2011

General comments:

This report is the outcome of a survey among leading scientists in the field. It is concise and well written, summarizing the sometimes different opinions and pointing up the questions where further research or action would be necessary.

Major compulsory revisions:

-

Minor essential revisions:

- there are a few incomplete sentences (e.g. the first one or one on p. 14)
- p.6, first line in HBCD: "(Law 2008)" - is this meant as a reference?
- at several positions in the text you have multiple mentioning of refs, e.g. [5,5,11,28] on p.12 or [27, 27, 51, 51] on p.15.
- shouldn't you use greek letters for the different HBCD diastereoisomers?
- please check your list of abbreviations (OctaBDE, pentaBDE is missing bromo-)
- please add the information on scoring values also to the legend of the first table
- there are a few typos left, please give the manuscript a final reading

Discretionary revisions:

- how/on which basis did you select the eight experts for the second questionnaire?
- maybe it might be better to have a table or a simple listing with the pros and cons of policy actions, to avoid repeating similar phrases (p. 17/18)?
- it is a bit astonishing that a comment on the methodology (the use of expert elicitation) appears as late as p. 19 and not earlier.
- the additional files 6 and 7 (policy brief) were originally written at which time? the text of file 7 says that Canada is going to publish a risk assessment in 2009 (and we have 2011 now) - is it possible to update or comment this?

Continue on a separate sheet if necessary

REVIEWER FORM TEMPLATE

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S7
Title	Policy relevant Results from an Expert Elicitation on the Human Health Risks of Decabromo-diphenyl ether (decaBDE) and Hexabromocyclododecane (HBCD)
Author(s)	Solveig Ravnum ^{1,9,§} , Karin E Zimmer ² , Hans Keune ³ , Arno C Gutleb ⁴ , Albertinka J Murk ^{5,6} , Janna G Koppe ⁷ , Brooke Magnanti ⁸ , Jan L Lyche ² , Gunnar S Eriksen ¹ , Erik Ropstad ² , Janneche U Skaare ^{1,2} , Michael Kobernus ⁹ , Aileen Yang ⁹ , Alena Bartonova ⁹ and Martin Kraymer von Krauss ¹⁰
Referee's name	Leo van der Ven

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

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3. Are the data sound and well controlled?
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5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

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- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

This expert elicitation addresses human health risks of two widely used brominated flame retardants, decaBDE and HBCD. The issue is highly relevant in view of the environmental burden of these compounds, and in view of published health hazards. The method of expert elicitation is presented as “a rapid assessment tool aimed at highlighting areas of agreement and areas of disagreement on knowledge-related key issues for environment and health policy making”. The authors also state that “The ... method ... is not intended as a substitute for risk assessment”, although they identify advantage of their method over consensus reports, particularly to identify areas of (dis)agreement among experts.

I am very confused about the value of this report. The “Introduction and Aims” is particularly comprehensive on the HENVINET project in general, but rather short on the specific aim relating to the two selected compounds, i.e. what is the justification of applying the method there? Are uncertainties not sufficiently identified and addressed in existing consensus reports such as the EU RARs on these compounds, and in existing publications? Remarkably, the RAR

on decaBDE [European Union Risk Assessment Report: bis(pentabromophenyl) ether] and its update(s) are not referenced at all, nor is the recent EFSA Scientific Opinion on Polybrominated Biphenyls (PBBs) in Food. Similarly, although the outcomes of the applied method are underpinned through specific references, there is no evaluation of the conclusions of the expert elicitation against conclusions of existing consensus reports.

Then, what should be done with the concluded agreement and disagreement? Does the agreement reflect the current state of the science? Is that also true for the disagreement or does that mainly reflect differences of expertise?

I have also major concerns about the expert elicitation method itself. There is no information on the composition of the phase I and phase II expert groups, nor on the individual expertises. Was there a balanced input from toxicologists, epidemiologists, chemists, etc? Was the invitation to contribute open or targeted? Was weight of the input of a toxicologist on exposure issues similar to that on hazard issues? Were all experts at a similar level of knowledge on these compounds (were authors of consensus reports included), were they really representative of the field? In that respect: I was also invited to participate and the invitation stated: "Participants will be acknowledged (if they prefer so, anonymously)."; now in this report, there is only a general acknowledgement to first questionnaire respondents, which does not comply to the original promise. And consequently, the reader cannot assess the level of expertise of the group. The method is presented as a scientific tool, which I doubt in view of the above concerns. I acknowledge that it is important to bring experts together to evaluate the state of the science on emerging topics, and identify knowledge gaps, but be realistic on the ambition and the value of the format. There is no apparent weight of facts, just a weight of opinions. Therefore, for this report, it is sufficient to explain the work flow, summarize the outcomes and assess these against existing (consensus) reports. In its current form, the text is too talkative (too many non-essential details, informal language ("the experts said", "the experts meant"), while major issues: are the current consensus reports up-to-date, do they reflect current concerns, are insufficiently addressed.

Finally, the manuscript could have been taken care of better before submission for review. There are many grammatical errors, e.g. improper use of present tense (all observations and conclusions should be in past tense, e.g. p16, halfway: "the experts consider", p18 "policy actions are justified"; improper conjugations (e.g. p6 "Concentrations ... has increased"; p16: "Third, studies was prioritized") and other singular/plural mistakes (p4: "...on phthalates, another chemical substance..."). There are no Figure captions, fully incomprehensible phrasings (e.g. Table 3 heading), sloppy reference list ("Ref Type"??? at ref 12, 13; name misspellings in many refs, e.g. Van BR in ref 35, van d,V, and van de KT in refs 36, 37, Van VM in ref 47 etc).

Major compulsory revisions:

Rewrite and condense the manuscript; focus on major message, omit details. Justify evaluation of the two selected compounds. Explain the work flow, do not present that as methodology. Evaluate conclusions against existing reports. Revise language.

Methodology: provide a work flow, restrain from suggesting this as an accepted, validated method. (The method is far from completed, see comments from participants); define the "experts" (what expertise do they represent).

Minor essential revisions:

p9: explain "not all of the answers were save"; "for some sections"

p10: what is meant with: Data on this has been reviewed.?p13: a-, b-, g-HBCD (Use greek symbols!! throughout) are not metabolites, as implied by the following phrase: "and other metabolites"

p15: first line: health risk instead of health impact?

p15: halfway: delete "Already"

p15: lower brominated, instead of: less brominated

p15: excreted, instead of: excreteted

p16: "there is insufficient data available for this compound and less than e.g. for decaBDE": less than, how was that assessed??

p17: "a couple of": unscientific language

p17: "there have been done some estimations of exposure": grammar

p17: shown for HBCD, not showed for HBCD

p18: 1c) this is a rather unconventional risk-benefit analysis which needs scientific underpinning, e.g. there is material to substantiate "prevent a few deaths"; does this expert imply that policy makers should choose to accept "a few deaths"?

p18: analogue compounds?

p18: BFRs are also POPs

p18: the amount of human exposure: try to find a better expression

p19: to organise ... better: try: improve the organization of

p20: priority issues ... were selected: meaning identified?

Table 3: define all terms (frequency, ranking in total etc) and match terms in table heading and in lower table proper.

Fig. 1 is not self-explanatory, e.g. colors in second row boxes (yellow – green – pink – light blue) suggest a relation/connection, which is not evident.

Discretionary revisions:

2nd review of Leo van der Ven of article number 1476-069X-9-S1-S7

Compared to the previous version, this manuscript is in much better shape now. The work flow is clear, the ambitions of the exercise are stated properly. It is now an attractive report, nearly ready for publication.

Minor comments:

Although language has much improved, and the text runs fluently, it should be critically reread on the following:

- punctuation
- grammar still not perfect, see e.g.: Concentrations of HBCD in the environment has increased (HAVE increased)
- typos (e.g. se instead of see)

Talkative language is now largely replaced, although some phrasings could be "professionalized", e.g. some young and more experienced; consider: junior and senior

Finally:

- remove webaddress if not publicly available:
<http://henvinet.nilu.no/EvaluationofKnowledge/tabid/1333/language/en-US/Default.aspx>. Login required.
- Reference list needs further attention, e.g. "van der SJ, Kloprogge P" in Ref 7 is probably wrong; also "Ref type" is included in many Refs

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S8
Title	Interaction of xenoestrogens and estrogen related cancers:reproductive system, breast , lung, kidney, pancreas and brain
Author(s)	Fucic et al
Referee's name	Janna Koppe

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:This is a good article can be accepted

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions: only a few typo's

Continue on a separate sheet if necessary

This is an excellent article, easy to read. By email I have send a few typo's to the author.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S8
Title	Interaction of xenoestrogens and estrogen related cancers: reproductive system, breast, lung, kidney, pancreas and brain
Author(s)	Fucic et al
Referee's name	Gutleb AC

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

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2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

A well-written manuscript that need only some editing. I have made comments directly into the manuscript.

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions:

All typing errors I found you will find in the manuscript that the editor will provide.

Referee’s comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S9
Title	Cancer risk and the complexity of the interactions between environmental and host factors: Henvinet interactive diagrams as simple tools for exploring and understanding the scientific evidence.
Author(s)	Merlo et al
Referee’s name	Janna Koppe

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: This is a good article I have only minor remarks, see text.

Major compulsory revisions:

Minor essential revisions:

See below

Discretionary revisions:

Also this second article from your group is in my opinion a very good article and thanks to Arno my task for small typo's was easy. What a lot of work you also did for Henvinet. This article is clear to a person like me, that doesn't know much on cancer in general. So congratulations with this excellent work. However the email addresses of all authors must be given, see the instructions for authors, and two typo's Arno hasn't found: in the abstract line 11 an "r 'is missing in the word referring and last line of the abstract sama must be same. I had also problems like Arno with the left lines of figure 8 and 9 using two different printers, as he has told you. To my happy surprise I read that Franco and you made a nice pyramid, on medical research and you put meta-analysis as the ultimate proof, but you didn't mention animal studies, but as it is for me it is ok and you are right about the meta-analysis putting that on top. I remember how Franco became cross with me about how to test pollutants and I told that the randomized controlled trial was the only proof. So I like the pyramid very much, because it put what we do in perspective. Again in general the article is very nice work, please tell Franco about this, because I don't have his email, can you forward this?

Janna

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S9
Title	Cancer risk and the complexity of the interactions between environmental and host factors: HENVINET interactive diagrams as simple tools for exploring and understanding the scientific evidence.
Author(s)	Merlo et al
Referee's name	Gutleb AC

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

A well-written manuscript that need only some editing. I have made a few comments directly into the manuscript.

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions:

All typing errors I found you will find in the manuscript that the editor will provide.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S10
Title	Thyroid hormone metabolism and environmental chemical exposure
Author(s)	Koppe et al.,
Referee's name	Gutleb A.C:

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

A well-written manuscript that need however some editing. I have made comments directly into the manuscript as the use of abbreviations, some statistical terms etc. is not consistent throughout the text.

Major compulsory revisions:

I suggest moving up the paragraph on PBDEs on page 6 right after the corresponding paragraph on PCBs.

Minor essential revisions:

Discretionary revisions:

All typing errors I found you will find in the manuscript that the editor will provide.

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S10
Title	TBB-A, thyroid hormone metabolism and effects of PBDEs on thyroid hormone
Author(s)	Koppe et al
Referee's name	Aleksandra Fucic

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
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- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: Manuscript gives significant added value in investigation of PCBs, dioxins and PBDE on disturbances of thyroid hormonal activity in children. Current data show the significance of analysis of wide spectra of pathways which may be deviated by chemicals which interact with estrogen and testosterone. Manuscript is significant contribution in the environmental health of children.

Discretionary revisions:

As PCBs are estrogen like compounds and as thyroid is embryologically of the same origin as breast it could be expected that metabolism could be similar. Consequently it would be worth to divide subjects in subgroups and see whether those subjects with CYP1A1 m2 with exposure after to polychlorinated biphenyls (PCB) differ in response (Charlier, 2004, Zhang, 2004, Moysich, 2002).

PCBs decrease levels of testosterone which increase immunological activity. However in case of PCBs there is suppression of T lymphocytes which indicate maybe unknown pathways. There is a tight correlation between levels of estrogen/testosterone and thyroid activity. Antiepileptic drugs which are in majority of cases aromatase inhibitors decrease levels of estrogen and increase testosterone and disturb function of thyroid.

I do suggest paper: Fujimoto N et al, J Endocrinol 2004, 181, 77-8 and Van Y et al., Environ Sci Technol, 2010)

Genomic and non genomic interactions of organisms with PCBs, dioxins and PBDE are very complex. PCB impact on endogenous estrogen disturbances could be mentioned in discussion.

Continue on a separate sheet if necessary

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S11
Title	Bladder cancer, a review of the environmental risk factors
Author(s)	Silvia Letašiová et al
Referee's name	Aleksandra Fucic

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: Manuscript gives review on bladder cancer aetiology related with environmental exposures and life style. Data on such causality are limited on arsenic and smoking. Cutting out of chapter on occupational exposure is suggested.

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions:

Continue on a separate sheet if necessary

Abstract, background: The first sentence should point whether aetiology of bladder cancer is not known or, are there available data on possible correlation with exposure, in any case more informative. **Results** Results on occupational exposure could be later mentioned but the title is environmental exposure. Delete data on occupational exposure. **Conclusion** Same as Results chapter. Please keep only information on environmental exposure. The last sentence has no meaning. What growing number of chemicals in occupational environment has with latency? Cancer latency is another story. Reformulate.

Introduction

Zeegers review can not be described as recent as it is published 11 years ago. Two Zeegers papers cited at the beginning of the chapter and in the end seem as contradictory. Please clarify.

Risk depends on the method of tobacco smoking: pure cigarette smokers were at higher risk (95 % CI 2.9 – 4.2) than pure pipe smokers (95 % CI 1.2 – 3.1) or pure cigar

In the chapter risk should be related with bladder cancer as written this was it is not clear...

Including of occupational exposures related with bladder cancer is questionable as the title is environmental exposure. I would suggest cutting out of this chapter or change of the title. Maybe title could be smoking and arsenic as environmental risks factors for bladder cancer

Please improve English

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S11
Title	Bladder cancer, a review of the environmental risk factors
Author(s)	Silvia Letasiova et al
Referee's name	Janna Koppe

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

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- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: Nice article

Major compulsory revisions:

Minor essential revisions: In the abstract the findings of hair dying also at home and by hairdressers must be mentioned.

Discretionary revisions: I have made a few typo's better in the text

Dear authors, this is a very nice well written article, easy to read and can be accepted. In the abstract however I think your findings in hairdresses and hairdying at home one a month in relation to risk of bladder cancer should be mentioned. I have made some little changes and typo's in the text that I attach.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S12
Title	Associations between environmental factors and incidence of cutaneous melanoma. Review.
Author(s)	K.Volkovova, D. Bilanicova, A. Bartonova, S. Letašiová, M. Dusinska
Referee's name	Aleksandra Fucic

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

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- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: Good, very informative article

Major compulsory revisions: Authors are kindly asked to improve manuscript following included comments and corrections. Abstract and Conclusion have to be rewritten.

Continue on a separate sheet if necessary

Dear authors, this is a very nice well written article, easy to read and can be accepted. In the abstract however I think your findings in hairdresses and hairdying at home one a month in relation to risk of bladder cancer should be mentioned. I have made some little changes and typo's in the text that I attach.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S12
Title	Associations between environmental factors and incidence of cutaneous melanoma. Review
Author(s)	Katarina Volkovova et al
Referee's name	Arno Gutleb

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

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2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
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- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: Good article but will need a language check and some shortenings of parts not related to cancer and UV etc. At some places too detailed. All added with track changes into the manuscript.

**Major compulsory revisions:
Please rearrange the paragraphs in question**

Minor essential revisions:

Discretionary revisions:

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S12
Title	Associations between environmental factors and incidence of cutaneous melanoma. Review
Author(s)	Katarina Volkovova et al
Referee's name	Janna Koppe

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

Major compulsory revisions:

Minor essential revisions: some changes in the text and language might be done, I will send the text with my supposed changes in red, otherwise the article is very informative. The part on genetic changes and polymorphism is for me difficult to read.

Discretionary revisions:

Dear author, this is a very clear article addressing an important problem. I think it can be accepted after minor revisions. A glossary would be very helpful. And you must be consequent, I mean it is either UVA or UV-A but not both. Since I am not an expert in malignancies I am not able to review the genetic part so well, lots of abbreviations are used there that makes the chapter not so readable. I have some suggestions to make the text more readable in red and send that separately.

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S13
Title	Nanoparticles in the environment: assessment using the causal diagram approach
Author(s)	Rahman et al
Referee's name	Elke Dopp

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: The paper gives an useful overview about the toxicological and environmental effects of nanoparticles (NP) in general, about distribution and exposure scenarios as well as possible consequences. The increasing use of NP is for sure an environmental and health problem but if we want to correlate exposure and health effects we have to account for concentrations. Toxicological effects are always concentration-dependent. The statement in the paper that “NP have existed in the environment since the beginning of Earth’s history...” is undoubtedly correct and if we want to discuss cause-effect relationships we have to care about harmless background concentrations and harmful overload conditions. At least examples and some references should be given (there are many NP measurements in air available and this is related to health effects e.g. cardiovascular effects) Also NP measurements in human organs and fluids are available.

Major compulsory revisions:

Health effects are listed in Fig. 1 but neurotoxic effects are missing. It is very much simplified to conclude that NP exposure causes toxicity by ROS formation and apoptosis. There are much more cellular mechanisms involved in NP toxicity and this depends on many factors.

Minor essential revisions:

-Page 8, last sentence:deaths per year caused by asian brown clouds are mentioned. It should be added in one sentence why asian brown clouds cause death.

-page 9, last sentence of first paragraph: human cancers are mentioned. The authors should specify which cancers are meant (skin cancer?)

-page 12: NP in food is a big problem because it is used routinely already and can be found in yoghurt, ketchup, low-fat cheese etc. in high concentrations. More informations about NP in food and possible health effects by intestinal uptake should be given.

-Fig. 2: Why are viruses a source of NP release?

-Fig. 4: Why are OH-radicals are decreased? They are increased!

Why is exposure to UV sunlight increased? The picture before (Fig.3) shows an “Decrease in sunlight intensity”!

“Incidence of cancer” is too general. Which cancer is meant?

-Fig. 5: “Various allergic diseases” is too general. Some examples (+ reference) should be given.

-Fig. 7: What is the source of the upper picture? Give reference!

Discretionary revisions:

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S13
Title	Nanoparticles in the environment: assessment using the causal diagram approach
Author(s)	Suchi Smita, Shailendra K Gupta, Alena Bartonova, Maria Dusinska, Arno C Gutleb, Qamar Rahman
Referee's name	Philipp Rosenkranz

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
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Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

→ See separate document

Review by Philipp Rosenkranz of the article ‘Assessing environmental health related to nanoparticles using a complexity approach’ by Qamar Rahman (lead author)

General comments:

The authors describe in their manuscript called “Nanoparticles in the environment: assessment using the causal diagram approach” a method to assess environmental effects of nanoparticles via a visual tool called causal diagram. A review of publications dealing with sources of natural and engineered nanoparticles and their effects on the atmosphere, various biological matrices and human health is presented. Several causal diagrams are shown, linking sources, route of exposure and effect of nanoparticles together.

I quite enjoyed the very broad about nanoparticles in the atmosphere since it included much information previously not known to me.

However, I see three major weaknesses of this manuscript:

- A detailed methodology is missing
- Findings from the literature are often generalized
- The authors focus much on atmospheric effects, not describing the remaining environmental matrices sufficiently

Therefore my recommendation for this manuscript has to be:

Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

In the following paragraphs I will try to give a more detailed description that lead to these conclusions

Major compulsory revisions:

A detailed methodology is missing:

A very brief methodology is given as part of the abstract but a methodology section in the main manuscript is missing. I understand that a more thorough description might be given in an additional manuscript of the same supplement. However, a brief description is also needed in this manuscript. In the present state a link between the findings in the literature and the presented causal diagrams is missing. The methodology part should include (but not be limited to) criteria for effects or pathways to be included in a causal diagram and how the method is able to identify knowledge gaps and aid further research. The first point is necessary for researchers who want to replicate similar diagrams, the second point is mentioned several times in the manuscript but no reasoning is given.

Findings from the literature are often generalized

Firstly, nanoparticles are very diverse. They are derived from different “parent bulk materials” with different characteristics. The only thing all of them have in common is, that they have one, two or all three dimensions below 100nm. One particle might be able to translocate into cells due to size and surface charge, for another one this might not be true for the same reasons. A general assumption, what is true for one particle is also true for all nanoparticles cannot be made.

General assumptions like this appear several times in the review part of this manuscript:

Impact of NPs on human health by ROS generation was found one of the major pathways leading to development of various diseases. (Page 2, Line 46-48).

As the sentence stands now, it means all NPs produce ROS and as it is rightly explained later in the text, this is a possibility for some of them, but not necessarily all. A good overview over which particles have a potential to produce ROS and therefore can cause oxidative stress is given in Reference Nr [6], Navarro et al., 2008.

NPs enter the plants via the root cell walls (Page 10, Line 214) Same as above. Which NPs can enter the cell? A reference is needed here to justify this sentence. If this sentence refers to Reference Nr [6], several sentences later, it should be stated that there is a **potential** for NPs entering the plant via the root cells

Using embedded transport carrier proteins and ion channels, NPs enter the cell and interfere with normal metabolic processes. (Page 10, Line 217-219). The cited reference reads: The ENPs also **might** cross the cell membranes using embedded transport carrier proteins or ion channels. As soon as the ENPs enter the cell, they **may** bind with different types of organelles.... (Navarro et al., 2008).

There is a huge difference between those two statements.

Asian brown clouds carry large amounts of soot and black carbon which are deposited on the glaciers, allowing them to absorb more of the sun’s heat and melt quicker (Page 8, Line 150-151) The cited reference reads: ... with **predicted** effects including changed circulation and monsoon patterns with amplified droughts and floods (10, 11), as well as increased melting of Himalayan glaciers (Gustafsson et al., 2009). The article didn’t assess glacier melting, but just predicted it. Therefore it can’t be concluded that the glaciers are already melting

largely wood and animal dung used for cooking and mainly contains particulate matters and carbon NPs from unprocessed fuel [28]. (Page 6, Line 142-143) The cited reference

didn't evaluate if nanoparticles were present in the analyzed samples. Although I agree that possibly a substantial part of the soot contains nanoparticles, a reference analyzing the size distribution of particulate matter in brown clouds has to be found. This is quite essential, because otherwise the effects observed in Line 143-147 cannot be linked to be a problem of nanoparticulate matter but rather the bulk material itself which happens to have a nano sized fraction. The same is true for reference [12]. The paper evaluates possible transport of microbiota via dust events. The report doesn't state anywhere in the article that the dust consists of "several millions of tons of natural NPs" (Page 4, Line 95).

One of the aims of this manuscript is an assessment of nanoparticles in the environment. The authors have to carefully choose references for their arguments that assess the effects of nanoparticles, not particulate matter in general

The authors focus much on atmospheric effects, not describing the remaining environmental matrices sufficiently

Without a doubt, the mechanisms and effects of nanoparticles in the atmosphere described here by the authors are important and dust clouds as well as brown clouds are discussed intensively. But since the manuscript aims to assess effects on the whole environment, an equally detailed discussion of the three remaining matrices is needed. While plants receive a certain attention, invertebrates are just mentioned by the example of nematodes. Higher organisms (excluding humans), as for example fish, only appear in Page 4, Lines 74-76. Here I would prefer the authors to give a more complete picture.

This is also reflected on the causal diagrams. For example on Figure 1: Is accumulation in a biological matrix the only effect of nanoparticles in Soil, Water or Sediment?

Minor essential revisions:

A couple of minor revisions needed are:

Page 5, Line 116 Titanium is a metal. The sentence needs to be rephrased

Page 5, Line 118-120 It needs to be discussed here that the effects of the described carbon nanotubes are not because they have 2 dimensions in the nanoscale, but because they can behave similar to asbestos (see Poland et al., 2008). This also becomes important on Page 11, Line 229-230. Reference Nr 45 observed the TiO₂ and CeO₂ just on the root surface while the MWCNT were able to penetrate the cell. MWCNT are nanomaterials but the penetration happened because they also show asbestos like behaviour.

Page 6, Line 146. This statement needs a reference

Page 8, Line 166-170. This paragraph needs references. If all statements refer to [27], then the paragraph needs to be rephrased to make this clear

Page 9 Line 174-184 and Figure 4. It has to be clarified, that this paragraph (and Figure 4) refer to the Atmosphere and not to the environment as a whole. Free hydroxy radical concentration in a natural water body or in biological active soil possibly tends to be near 0. Furthermore, it has to be considered that certain nanoparticles potentially produce ROS. The hydroxyl radical is an ROS (see also Donaldson et al., 2005: Combustion-derived nanoparticles: A review of their toxicology following inhalation exposure)

Page 9, Line 187-188. This statement needs a reference

Page 9, Line 188-189. This statement needs a reference

Page 12 Line 268-269. A reference is needed here

Discretionary revisions:

Page 3 Line 68. A definition of indirect exposures would be beneficial at this point

Page 4, Line 77. "there is potential agreement and disagreement" this sounds strange. Can this be rephrased somehow?

Page 5, Line 101. The annual release of ENPs into the environment cannot be estimated. This was attempted by other authors already. The following references might be useful.
See: MUELLER, N. C. & NOWACK, B. (2008) Exposure modeling of engineered nanoparticles in the environment. *Environ Sci Technol*, 42, 4447-53.

And

DEPARTMENT FOR ENVIRONMENT FOOD AND RURAL AFFAIRS (DEFRA) (2007)
Characterising the potential risks posed by engineered nanoparticles: a second UK government research report. London, UK, Department for Environment, Food and Rural Affairs.

For the special case of Titanium dioxide, some information here:

U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA) (2009) Nanomaterial Case Studies: Nanoscale Titanium Dioxide in Water Treatment and in Topical Sunscreen. EPA/600/R-09/057. Washington, DC, U.S. Environmental Protection Agency.

Page 5, Line 107 and Page 13 Line 281. As a growing and widely applied science, nanotechnology has a global socioeconomic value. This sentence appears twice. Rephrasing one of them might be a good idea

Final remarks:

The authors try to tackle quite a complicated and diverse issue by assessing effects of nanoparticles in the whole environment. To achieve this, more attention needs to be paid to the non atmospheric matrices with all their complexity and interactions. This would eventually make the proposed causal diagrams very complicated, maybe even too complicated to be considered as useful tools to identify knowledge gaps. In order to establish causal diagrams as a method for problem finding and problem display and to advocate communication, sometimes less can be more. From my point of view, it may be a better approach to concentrate just on one matrix and show, just briefly, interferences with the other matrices, if and when they occur. This would allow a more thorough discussion of the matrix focused on without making links too complicated. In my opinion the best choice would be here nanoparticles in the atmosphere. The steps between the initial review of the appropriate literature and the final product, the causal diagram, have to be explained better. A thorough reading of the cited literature to ensure the focus stays on effects of nanoparticulate matter -and not particulate matter in general- is also advisable.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S14
Title	A healthy turn in urban climate change policies; European city workshop proposes health indicators as policy integrators.
Author(s)	Keune et al
Referee's name	Gutleb AC

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

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5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

A well-written manuscript that needs only some editing. I have made comments directly into the manuscript.

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions:

All typing errors I found you will find in the manuscript that the editor will provide.

Referee’s comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S14
Title	A healthy turn in urban climate change policies; European city workshop proposes health indicators as policy integrators
Author(s)	Keune et al
Referee’s name	Aleksandra Fucic

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Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: Paper is very interesting and gives important insights in the topic. It has fresh approach and could be interesting and understand within several interest groups. It is written in fluent and dynamic style.

Major compulsory revisions:

Introduction is far too long. All copy/paste parts from papers and reports should be deleted, instead, their content should be described and comment.

Methods must begin with short description of backcasting within one chapter as it is too long.

Minor essential revisions:

Discretionary revisions:

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S15
Title	The challenge of social networking in the field of environment and health
Author(s)	Van den Hazel et al
Referee's name	Janna Koppe

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: good article, can be accepted as it is, only a few typo's

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions: It might be shortened. There are only a very few typo's, two times form is typed when from is mentioned, but because the paper is not numbered it is difficult for me to tell the author where that is. Please go over the paper again for little typo's.

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S15
Title	The challenge of social networking in the field of environment and health
Author(s)	Van den Hazel et al
Referee's name	Aleksandra Fucic

When assessing the work, please consider the following points, where applicable:

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- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

Manuscript is giving clear overview on activities and workshops organized by HENVINET. Methodology, results and discussion are going to be interesting source of information for subjects involved in environmental health but also for students as it gives insight in the process of social networking important in application of scientific results in practice.

Major compulsory revisions:

Minor essential revisions:

**There are typewriting mistakes which should be corrected.
 Additionally sentence on page 9 1.line “The role is key...” should be rewritten.
 Page 12 sentence “The experts asking for more research and the local authorities waiting for a decision” should be rewritten.
 Page 14 “The methods are reasoning for this approach are fully explained in Keune et al., 2010.” Sentence should be rewritten**

Review Hans Keune paper Applying Social Media Approaches to Communicate Environment and Health. Results of a survey.

I have some main concerns with this paper:

1. It discusses the web portal but only in general terms and in terms of the survey; the latter only deals with it in a rather abstract and superficial manner and only reflects the views of a limited survey of which the respondents group is rather biased. I would propose to give it more flesh to the bone by adding information on the portal itself, e.g. on its actual development and use; e.g. I think we could be more informative on the difficulties that occurred when developing it and showed in the actual use: that's very informative wrt such endeavor. This would give readers a clearer view on what the portal is and make the discussion more interesting. This could also help create a better balance between content/data/analysis and the discussion section; the discussion section now is rather long compared to the actual research/survey section.
2. The method and results of the survey could benefit from being described more clearly and precisely and could do with some extra information. In the description of results it is not very clear (mainly at the end) that (if?) respondents could only have one vote. So the results show a kind of prioritization, which not all means that they would consider other issues unimportant, be it less when they have to choose. So please be more careful with how you describe the results. Also btw you should include non-response info. Moreover I guess that some kind of clustering of results (within one question, as far as answer categories are similar in a specific respect; not all categories are exclusive) that can be qualified within a broader analytical category of answers (answer categories that can be grouped and distinguished from another group), which could perhaps give you some extra room for interpretative maneuver. One example being in Q3: I cannot myself easily choose here, but in the survey we were forced to choose: prioritizes, but for me it does not mean that I want to exclude. What adds to the lack of clarity is that you refer to figures that do not actually visualize results, but merely show the options the respondents could choose from. Visualizing results in graphs could help I guess. Further more if possible I would add some information on the discussion about the results of the voting: after each presentation of results, a brief discussion was done with the audience. One specific (and informative to the analysis) example being the discussion on the answer category reflecting critically on the traditional evidence based culture: though prioritized by a relatively big proportion of respondents, when discussed with the group, it seemed that no one really could easily articulate what it means (in fact the micro was given to me, as I initially proposed the category when designing the questions). This is not a disqualification of the result as such, but merely shows that this is not an easy topic, while simultaneously it represents a general feel for a need to alternatives (important and informative result I guess). Another issue that might be informative is to characterize the results by type of respondents: is it possible to link the data from the survey? You have information from each voter on both the personal background (like scientist or policy maker) and on their preferences: can you link these?
3. Some important words could benefit from more clarification. What do you exactly mean by science – policy interface? As an illustration: the opening sentence of the paragraph Science-

policy interface on p8 is rather vague. Sometimes you even use 'the science – policy' interface as if this exists, somewhere (the portal?)? Or do you merely use it as a concept? Or both? And do you characterize this as a kind of a structural thing (e.g. IPCC) or as communication or as collaboration between scientists and policy community representatives in general? Also the use of words like expert, stakeholder, scientist, policy maker should be defined, distinguished and used more clearly. Now you seem to mix these categories. Btw, many policy makers can be considered to be experts as well as scientists. One example: what do you mean at p7 by stakeholder analysis? I should be a characterization of the respondents, but do you consider them all to be stakeholders? See also bottom p9: who are the stakeholders? And how do you distinguish multi-, inter- and transdisciplinarity?

Some specific issues:

- Description on p2 of critical discussion on traditional evidence based culture is too vague.
- In the next sentence on DSTs I do not understand the word 'also'. And in the sentence thereafter I do not understand the 'however'.
- On p3, what do you mean with broader view and broader communication?
- P8: majority – 41% ... ?
- P8: still, 34% ... does that necessarily contradict?
- P9: is there actually lack of interdisciplinary workgroups (strange word) ?
- P9: they also agree ... they is the 36%?
- Discussion section:
 - o Opening sentence is vague
 - o You start by disqualifying the extent to which the survey is of informative value, yet it represents the main topic of the paper...perhaps you better argue why you in fact do consider it of informative value?
 - o You use a lot of 'might be' ...
 - o It lacks critical (and relevant) reflection on the difficulties of developing and maintain such a portal
 - o P13: Issues like user.... This section is vague.
 - o The last part of this section seems to limit the science – policy interface to mainly one-way communication from science to policy. And it also disqualifies the expertise of policy makers wrt to the use of DSTs: what do you mean by 'proper use'?
- Conclusions section: I think this should be linked more clearly to both the results and discussion sections, and preferably also to the real practice of the portal.
- Wrt to the section describing WP 1 (knowledge evaluation) results, please refer to the relevant publications in the special issue on the method and the specific topics.

**Applying social media approaches to communicate Environment and health.
Results of a survey – comments on an article draft**

The article challenges the old problem with science supporting policymaking, especially how social media approaches can contribute to this process. In general I am very positive in new processes/products/services in this area. However, I start with some critical comments in order to improve the draft article text.

1. Define “traditional evidence based culture”
2. The article focuses on networking and E & H sources, increasing the *accessibility* to scientific information. The real problem with *communication* is only addressed marginally. Communication includes considerations on target groups, issue framing, timing, choice of media and establishing relations with policy makers. The survey is of limited due to the focus on networking, sources and decision support tools, and the majority of participating scientists in the survey.
3. The added value of the HENVINET portal, compared with ordinary Google search should be described.
4. The role of intermediaries between science and policymaking is not mentioned at all. World Health Organisation, European Environment Agency and the scientific committees of Dg Sanco is not mentioned at all.
5. The evaluations of causal chains of priority diseases are illustrative and an improved basis for decision-making.
6. The added values of social media approaches are not convincing. On the other hand the added value cannot be evaluated without pioneering efforts followed by asking the users about their experiences.
7. In vain, I have tried to get access to www.henvinet.eu several times between 6th and 13th February. Is the website operative?

Stockholm 13th February 2011-02-13

Ingvar Thorn

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S17
Title	Facilitating knowledge transfer: decision support tools in environment and health
Author(s)	Hai-Ying Liu ¹ , Aileen Yang ¹ , Panagiotis Neofytou ² , Christos Housiadas ² , Emanuele Negrenti ³ , Michael J. Kobernus ¹ , Alena Bartonova ¹
Referee's name	John G Bartzis

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

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Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

1. Is the question posed by the authors new and well defined?

The question that the authors pose is not quite new but there is an effort to give an answer to a problem with a high degree of complexity and the results are encouraging

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?

The nature of the problem is such that it is difficult to go to the desirable level of details. The overall approach and methodology is appropriate and complete to a large degree. It will be helpful though to be as clear as possible. I would suggest to include a table with appropriate text defining the selected DST (at least title and type).

3. Are the data sound and well controlled?
The data are appropriate and seem to be well structured
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data?
Yes
6. Do the title and abstract accurately convey what has been found?
Yes
7. Is the writing acceptable?

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S17
Title	Facilitating knowledge transfer: decision support tools in environment and health
Author(s)	Liu et al
Referee's name	Steinar Larssen

When assessing the work, please consider the following points, where applicable:

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Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

Discretionary revisions:

See comments in article.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S18
Title	Considering the cumulative risk of mixtures of chemicals – a challenge for policy makers
Author(s)	D.A. Sarigiannis et al
Referee's name	Sieto Bosgra

General comments:

The present paper reviews the methodologies to account for health risk of exposure to combinations of toxicants. It covers a wide range of domains, from current fundamental insights in effects of combinations of chemicals and how to predict those, to approaches for cumulative risk assessment, to how these may be incorporated in the risk management of combined health effects, and from assuming absence of interactions to accounting for their (possible) presence.

The latter – the step from more fundamental mixture toxicology to risk management options – is a valuable one, and distinguishes this paper from previous reviews on the topic. It provides a useful recommendation to policy makers that makes use of the currently available methodologies, but leaves the door open to the use of “21st century”-type toxicological information that may become available in the future.

Two general comments on this point:

- (1) It would help the reader to know that the current knowledge and cumulative risk assessment methodologies are reviewed in light of their applicability in regulatory frameworks, and that a proposed pragmatic solution to the problem awaits in the end. This could be stressed more in the abstract and introduction, and maybe even in the title.
- (2) A review that covers such a broad range of domains must be clear in its definitions, context and domains of applicability of the described methodologies to avoid confusion. Some improvements on this point are suggested below. In my experience, from a mixture toxicology point of view each methodology to predict cumulative effects or to detect interactions has its limited applicability under specific conditions that cannot be generalized. In risk assessment/management the viewpoint is much more pragmatic, and given the overall uncertainties an approximation (or worst-case, but not overly conservative) of the cumulative effects is usually good enough. This distinction could be more clearly indicated in sections 2 and 3, and in the transition between these sections.

Major compulsory revisions:

In mixture toxicology/risk assessment, the definitions of the terms expected effect, additive effects (dose~, Loewe), deviations and interactions are still confusing if not controversial. The paper would benefit from a clear definition of terms or from adopting terminology from any reference and stick to it. For instance, the definition of no interaction in p.8 not very helpful.

Regarding the limitations of dose addition and effect addition (section 2):

Dose addition has been shown to only apply to conditions under which chemicals have similarly shaped dose-response curves. Effect addition originates from probability theory of independent contributions to the probability of an event occurring. Its applicability is mainly in quantal responses, e.g. number of animals or cells affected. Its application beyond that has not yet been properly addressed. Two references (Junghans, Faust) are mentioned that compare these two methods on quantal responses in aquatic toxicity studies. This puts much weight to those incidental findings, which cannot be generalized without discussion of the limitations of either method. I suggest that the limitations of the methods are discussed first in the appropriate sections 2.2 and 2.3, and the comparison between methods be discussed thereafter.

The paragraph on bottom p.10 – top p.11 contains some unjustified generalizations: no such general conclusions about underlying mechanisms can be drawn from the shape of the dose-response curve. As just one example, sigmoidal curves result from simple receptor-substrate reactions, and effects of such mixtures (in absence of interactions) are well described by dose addition.

Further, the notion here and on p.6 that a combination of chemicals below their effect concentration would result in no mixture effect is an old-fashioned one: it heavily depends on the assumption of thresholds. The NOAEL should rather be regarded as a dose below the toxicity study's "detection limit", and the more chemicals are added just below their respective detection limits, the higher the chance of their cumulative effect exceeding that limit. When assuming monotonely increasing dose-response functions, any dose above 0 has an effect (however small it may be), and combinations below no observed effect levels may very well be combined by either dose or effect addition.

In section 4, the logical order would be to start with a general discussion on interactions and their occurrence, then methods to determine whether interactions take place, then methods to account for them in cumulative risk assessment. In the general section, it should be noted that claims about the presence or absence of interactions in the literature strongly depend on how the author in question defined interaction. Most commonly, (dose) additivity is considered the expected outcome, and any deviations thereof are deemed interactions, whereas additivity may not have been expected in the first place (see Bosgra et al, 2009). This is mentioned only very briefly in the description of the isobole method (4.2), whereas the point is much more general. It would be most helpful to give this issue more emphasis in the introductory part of section 4, which may help the reader nuance the descriptions that follow of observed deviations from additivity in the literature. For instance, it is stated that observations from Nesnow et al. are notable, whereas only small deviations were found from effect addition, which may not even have been the proper expectation for those mixtures.

Minor essential revisions:

The abstract does not yet clearly state the paper's goal and the conclusion that one universally applicable approach does not yet exist, but that a pragmatic, tiered approach is proposed, and what this approach encompasses.

The first paragraphs of 2.1 (11 lines) belong to the Introduction. It could be rephrased to more clearly state the paper's objective. The actual discussion of methodologies starts with "A mixture effect ...".

References are lacking in 2.1 on cumulative assessment by dose addition, e.g. of organophosphorus pesticides and dioxins and dioxin-like PCBs.

Section 3 could use an introductory paragraph describing the transition from mixture theory to cumulative risk assessment in practice (see general comment). The approaches mentioned implicitly assume dose (or concentration) addition, and are more or less interchangeable. For instance, the MOE approach (3.3) is equivalent to the RPF/TEF approach (as demonstrated e.g. by Van der Voet et al. 2009 Food Chem. Toxicol. 47, 2926 - 2940). The major difference is at which stage to extrapolate from experimental data to humans: for each chemical separately (allowing different assessment factors for each chemical) or after combining their doses/effects (thus one assessment factor for all).

On top p.13, the described practice of calculating a reference concentration from a point of departure (with interspecies assessment factors depending on the number of different test species/trophic groups) seems to refer to a specific regulatory framework (ecotox?). A reference to the regulation should be mentioned, as this may not be common practice in some other frameworks.

On p.19 (4.2): the statement on the economy of the isobole method is either quoted out of context or incorrect. Starting from the dose-responses of the individual chemicals, one can find individual doses d_1 and d_2 that are equipotent, and then a mixture that satisfies equation 18. This single mixture can be tested against the hypothesis that its effect should be the same as that of the doses d_1 and d_2 of the chemicals individually. Mapping an entire isobole by finding all combinations that actually do give the same response may indeed be a costly business, but what would be the purpose of that?

Bottom p.28 (a): no statement can be made about the predictive power of this approach. Whether the predicted HI is anywhere near the true ratio between exposure and health limit depends on so many factors: e.g. whether dose-addition gives the zero-interactive effect, whether the magnitude of interaction is characterized correctly, the appropriate interspecies extrapolation. What can be said is that it may give a reasonable approximation if the appropriate data are available, and if not, allows (conservative) assumptions about combined effects and interactions.

Discretionary revisions:

The term "toxicity" should be replaced by "toxic potency" in some instances, e.g. mid p.6, bottom p.7, top p.8.

Top p.7: models for chemical interactions are described in section 4.

The manuscript must be carefully checked for missing spaces, I came across a lot on p.17-18, p.21, p.30-31.

Bottom p.20: Funny, I just came across an interaction model that may have beaten Clewell and Andersen (1984) to it: a model describing the reciprocal inhibition of CYPs by R- and S-warfarin stereoisomers (Luecke and Wosilait, 1979).

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S18
Title	Considering the cumulative risk of mixtures of chemicals – a challenge for policy makers
Author(s)	D.A. Sarigiannis et al
Referee's name	Gutleb AC

When assessing the work, please consider the following points, where applicable:

[USE THE APPROPRIATE QUESTIONS FOR THE ARTICLE TYPE TO BE REVIEWED – SEE Reviewer Guidelines above]

1. Is the question posed by the authors new and well defined?
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
3. Are the data sound and well controlled?
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
5. Are the discussion and conclusions well balanced and adequately supported by the data?
6. Do the title and abstract accurately convey what has been found?
7. Is the writing acceptable?

Please make your report as constructive and detailed as possible in your comments so that authors have the opportunity to overcome any serious deficiencies that you find and please also divide your comments into the following categories:

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- **Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)**

Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

Well written that need only the correction of a few typing errors. I attach a word files with my comments in track changes. They use some footnotes and I suggest to incorporate them into the text.

Major compulsory revisions:

Minor essential revisions:

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S18
Title	Considering the cumulative risk of mixtures of chemicals – a challenge for policy makers
Author(s)	D.A. Sarigiannis et al
Referee's name	Arno C. Gutleb

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Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments: Good article, suitable for those who like to read about formulas

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions: I have added a few more typos and agree furthermore with the comments of PvdH

Referee's comments to the authors– this sheet **WILL** be seen by the author(s)

Article ref no.	1476-069X-9-S1-S19
Title	Critical complexity in environmental health practice: simplify and complexify.
Author(s)	Hans Keune
Referee's name	Paul Cilliers

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Where possible please supply references to substantiate your comments.

When referring to the manuscript please provide specific page and paragraph citations where appropriate.

General comments:

I have worked through the paper and I find it interesting and clearly written. I did not find anything I wish to dispute and I like the idea of *critical complexification* very much!

If I have a comment, it is that some of the positions taken could be argued for or motivated better. In particular, the claims of critical complexity should be motivated stronger. Instead of just stating that it implies limited knowledge and a normative dimension, and should show *why* (non-linearity, the problem of reduction, temporality, emergence etc). Also when presenting the two “techniques” (AD and EE), it should be made clear why they are attentive to complexity (this becomes clearer later, but should be argued for when they are presented).

Major compulsory revisions:
none

Declaration of competing interests

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In the context of peer review, a competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Reviewers should disclose any financial competing interests but also any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

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If you can answer no to all of the above, write 'I declare that I have no competing interests' in the space on page 1. If your reply is yes to any, please give details on page 1.

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S19
Title	A critical complexity perspective to environment and health
Author(s)	Keune et al
Referee's name	Janna Koppe

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General comments: The paper is reviewed by Paul Cilliers and me. Hans has made adaptations, so I propose to accept it now, Janna

Major compulsory revisions:

Minor essential revisions:

Discretionary revisions:

Referee's comments to the authors– this sheet WILL be seen by the author(s)

Article ref no.	1476-069X-9-S1-S19
Title	Critical complexity in environmental health practice: simplify and complexify.
Author(s)	Hans Keune
Referee's name	Peter van den Hazel

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General comments: Good article, suitable for those who like to read about formulas

Major compulsory revisions:

Minor essential revisions:

In the text there are some questions raised. Overall a complex paper, but relevant to gain insight in complex issues

Discretionary revisions: in the text some questions raised;
redraft of abstract according to methods, results, conclusions; for clearer abstract

Continue on a separate sheet if necessary