This is a background paper for discussion.
It does not reflect the views of the Committee and should not be cited.

CC/2019/10

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Scoping paper on the synthesis and integration of epidemiological and toxicological evidence in risk assessments

Introduction

1. The Committees on Toxicity and Carcinogenicity (COT and COC) have recently published a joint report on synthesising epidemiological evidence (SEES)[1]. During their meetings the subgroup also discussed the possibility of synthesis of epidemiological and toxicological evidence (SETE).

2. Current approaches usually consider epidemiological evidence separately from toxicological evidence, and then combine information at the end, a common dose response relationship is often difficult to establish. There are several methods available for quantitative synthesis of epidemiological studies, which were reviewed in the SEES report. However, there are few methods for toxicological studies or for combining epidemiological and toxicological studies. Some work is underway at the international level at providing guidance on how to integrate toxicological and epidemiological evidence, however a brief search has shown that little has been published since the SEES report.

3. It would be useful for the Committees to provide clear guidance on approaches to integrate epidemiological and toxicological data, for use by the Secretariats and Members. There is also interest in this combined approach from the PHE Air Quality and Public Health team, who oversee COMEAP.

4. The following scoping paper provides an overview of the proposed scope of work, including some information, publications and international guidance documents/frameworks already available to the Secretariat. The chapters given below are a proposed outline of the future document to be developed by a SETE working group, whilst also providing some background information and links to guidance documents and frameworks on the proposed topics. In addition, proposed search terms are provided for discussion for subsequent literature searches.

5. While reading the document the Committee are asked to consider what kind of output they would like to see from the working group and what format would be considered the most appropriate, for example an internal document for the Secretariat and Members to use in future assessments, a general guidance document and/or framework or referral to existing guidance documents/frameworks. The Secretariat

[1] Report of the Synthesising Epidemiological Evidence Subgroup (SEES) of the Committee on Toxicity and the Committee on Carcinogenicity. Available at: https://cot.food.gov.uk/cotreports/cotjointreps/synthesising-epidemiology-evidence-subgroup-sees-report

considers that in the interest of transparency and document would require publication and therefore would require strong justification for a solely internally facing document.

Proposed outline and scope of work

Chapter 1

Introduction and background

6. Current approaches to risk assessments usually consider epidemiological evidence separately from toxicological evidence, and then combine information at the end, a common dose response relationship is often difficult to establish. There is some work underway at the international level at providing guidance on how to integrate toxicological and epidemiological evidence, however, the majority of the international guidance documents and frameworks focus on specific endpoints or chemicals.

7. The European Food Safety Authority (EFSA) and the Evidence-Based Toxicology Collaboration (EBTC) organised a Colloquium to develop an understanding of the best practices, challenges and needs for evidence integration in chemical risk assessment, focusing on hazard identification and combining multiple studies and end-points for dose-response modelling.

8. The Report of the Colloquium meeting on evidence integration in chemical risk assessment can be found here:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2018.EN-1396

9. The US Environmental Protection Agency (EPA) uses an integrated risk information system (IRIS) in their risk assessment approach, namely in the first two steps of the risk assessment process, hazard identification and dose-response assessment. The diagram on the EPAs website shows the integration of evidence for each health outcome as part of the draft development stage, however no further details are given on the practical application of the evidence integration.

10. The website to the EPAs IRIS approach can be found here:

https://www.epa.gov/iris

11. A review of the IRIS approach can be found here (Chapter 6 focuses on evidence integration in hazard identification):

https://www.ncbi.nlm.nih.gov/books/NBK230065/

12. The Organisation for Economic Co-operation and Development (OECD) applies an integrated approach to testing and assessment (IATA), relying on the integrated analysis of existing information and the integration of new information, taking into account the acceptable uncertainties. There is no one overall guidance, however numerous guidance documents on specific topics such as skin corrosion and irritation are available.

13. The website for the OECDs IATA can be found here:

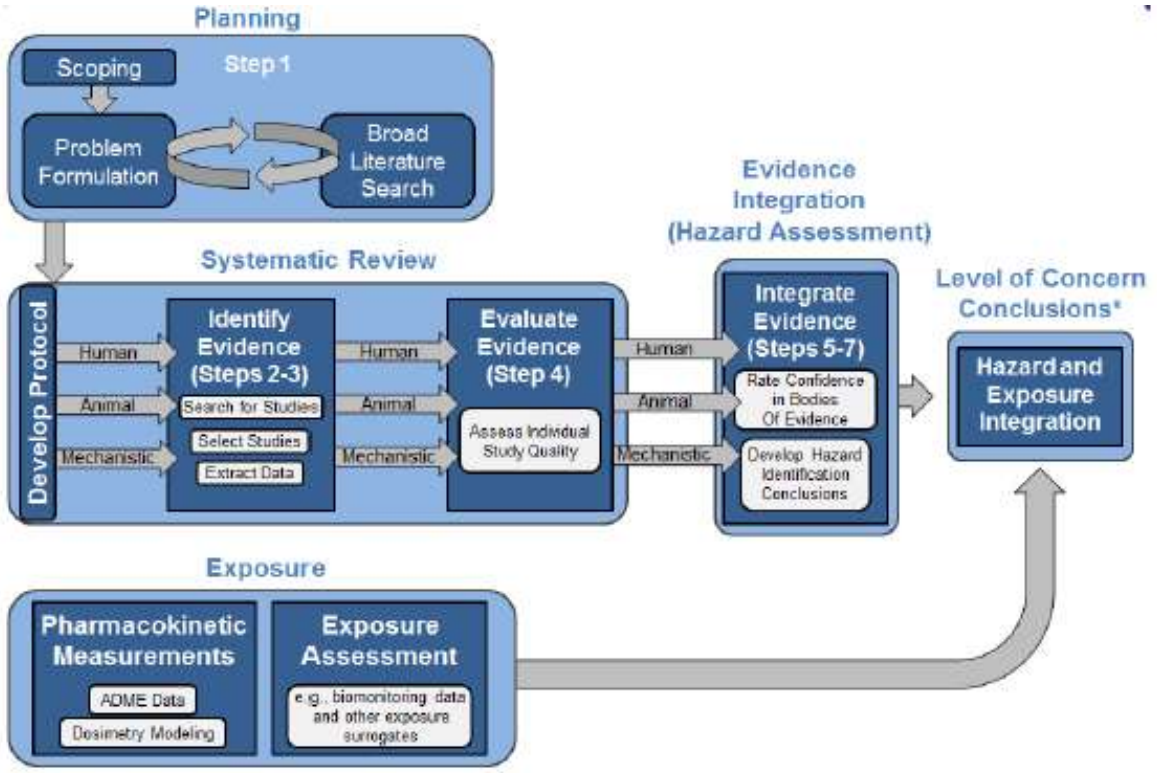
http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm

14. A report on considerations from case studies on IATA can be found here:

http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2018)25&docLanguage=En

15. In 2012, the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) started developing an approach for the implementation of systematic review methodologies to carry out evaluations about potential human health hazards. The updated handbook/framework (2019) provides procedures to integrate multiple evidence streams, and of specific interest here, a section on evidence integration to develop hazard identification conclusions (Step 7). Ideally, human data providing a high level of evidence are considered together with the conclusions drawn from animal data with a high level of evidence or mechanistic data, if they provide support for biological plausibility. The OHAT hazard identification labels are similar to the labels used in the Globally Harmonised System of Classification and Labelling of Chemicals (GHS).

16. Figure 1 gives and overview of the NTPs OHAT approach, all steps are described in detail in the framework.



ADME = absorption, distribution, metabolism, excretion
*NTP is currently updating the NTP approach for reaching level of concern conclusions (expected 2016/2017)

17. The website for the NTP OHAT systematic review can be found here:

https://ntp.niehs.nih.gov/pubhealth/hat/review/index-2.html

18. The 2019 OHAT Handbook, including updates and clarifications can be found here:

https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookdraftmarch2019.pdf

19. A paper by Rooney et al. (2014) summarizing and reviewing the framework developed by OHAT can be found here:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4080517/pdf/ehp.1307972.pdf

20. In 2006, based on previous experience, the International Programme of Chemical Safety (IPCS) produced a unified Human Cancer Relevance Framework (IPCS HRF) to provide a generic approach to analyse data and to contribute to harmonization. In 2008, the IPCS published a second framework considering other endpoints and non-cancer MOAs. Both frameworks start with the concept that it is sometimes possible to establish a causal path for a series of key events, whereby the key events are involved in the MOA. Once the MOA is established, qualitative and quantitative comparison of each key event between animal and human data enables a conclusion regarding the relevance of the MOA to human risk.

21. The website for the IPCS HRF and the frameworks as well as supporting documents can be found here:

https://www.who.int/ipcs/methods/harmonization/areas/cancer/en/

22. The integrated environmental health impact system (IEHIAS) website provides guidance how to carry out integrated environmental health impact assessments, combining epidemiological and toxicological evidence/data. The website provides a range of information on the various steps included in the framework, ensuring the assessments are targeted on the right issue

23. The website can be found here:

http://www.integrated-assessment.eu/eu/index.html

24. An assessment of the IEHIAS, including case studies can be found here:

http://www.integrated-assessment.eu/eu/sites/default/files/CCS_FINAL_REPORT_final.pdf

25. Vandenberg et al. (2016) proposed a framework for the systematic review and an integrated assessment (SYRINA) of endocrine disrupting chemicals (EDCs). The framework builds on existing methodologies and evaluates the evidence from individual studies, followed by the evaluation of each evidence stream and finally the integration of evidence across all streams. The framework aims to provide the evidence base needed to draw conclusions, make recommendations, evaluate the uncertainties and support decision making.

26. The full paper can be found here:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4944316/pdf/12940_2016_Article_156.pdf

27. Adami et al. (2011) propose a five step "Epi-Tox" process, bringing together the data and analysis from epidemiological and toxicological studies with the aim to provide a view on an adverse causal relationship between an agent and a disease. The process includes the quality assessment of each individual study, the assignment of scalable conclusions regarding the biological plausibility and evidence and the placement of the findings on a causal relationship grid. The framework also aims to identify and show the influence additional data can have on the potential outcome.

28. The full paper can be found here:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3155086/pdf/kfr113.pdf

29. Lavelle et al. (2012) proposed a framework for evaluating and integrating human and animal data in chemical risk assessment. The process includes a step wise determination and assessment of the quality of the available human and animal data. The evaluation of human data includes various quality elements and the nature and specificity of the lead effect, the evaluation of the animal data includes data quality assessment and relevance to humans. The integration of the human and animal data involves the comparison of the various quality ratings and the determination of which data can be used to create the risk assessment based on a set of principles, such as 1) best quality data should be applied, independent of human or animal origin, 2) human studies of high quality should take precedence, 3) several considerations if human and animal data are of equal quality and are concordant or not. The framework draws on previously proposed guidelines and provides a number of case studies.

30. The full paper can be found here:

https://www.sciencedirect.com/science/article/pii/S0273230011002029

31. Negri et al. (2017) applied an integrated approach to the assessment of PFOA and PFOS exposure to fetal growth. The results of the epidemiological and toxicological data showed a reduced body weight in both, humans and rodents, however, the effective extrapolated serum concentrations in animals were 10^2-10^3 times higher than those in humans. The authors therefore concluded based on the integrated data, that the toxicological data does not support the epidemiological association, thus reducing the biological plausibility of a causal relationship.

32. The full paper can be found here:

https://www.tandfonline.com/doi/abs/10.1080/10408444.2016.1271972?journalCode=itxc20

33. A publication by Boyes et al. (2005) looked at the integration of human (experimental and epidemiological) and animal data to evaluate the potential risk to human health from chronic exposure, focusing on neurotoxicity. The authors

suggested that the comparability and the consistency of outcomes across studies could be improved by considering functional domains rather than individual test measures. Currently, the abstract only is available, no details regarding the practical application could be given.

34. The abstract is available here:

https://www.ncbi.nlm.nih.gov/pubmed/17615109

35. The Scientific Committee on Consumer Safety (SCCS) provides notes of guidance for the testing and safety evaluation of cosmetic ingredients. Included in the guidance are general references to the IATA guidance but specific to the guidance on skin corrosion and irritation. It also touches on integrated approaches for cosmetic ingredients with potential endocrine activity and the usefulness of integration of *in silico* results with other sources, such as *in vitro* tests, to generate sufficient evidence to exclude potential toxicity.

36. The SCCS notes on guidance can be found here:

https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_224.pdf

37. All of the frameworks and publications described above have certain aspects or steps in common, such as 1) problem formulation 2) systematic literature review, including exclusion and inclusion criteria for data/literature extraction 3) quality scores of studies among the different endpoints, species, toxicological and epidemiological data etc and 4) quality scores across studies. The last two steps most commonly utilise the weight of evidence (WoE) approach, applying specific criteria and taking into account factors such as dose-response, biological plausibility, coherence and consistency, and finally the integration of all data (animal and human) to conclude on the effect or lack thereof.

Chapter 2

Weight of evidence approaches and scoring systems

38. Most of the guidance documents/frameworks mentioned in Chapter 1 apply a weight of evidence (WoE) approach in their evidence/data integration; described in detail in the respective papers.

39. In addition, there are a number of international bodies that have considered the WoE approach and issued guidance, such as EFSA, with the aim to evaluate the relevance, reliability and consistency of all evidence. Similar to the frameworks and papers on data integration in Chapter 1, the documents on the WoE approach covers a number of steps, such as question formulation, weighing the data within one line of evidence, such as endpoints, species etc and the integration of all data across the lines of evidence.

40. Links to some of the guidance documents can be found below:

EFSA
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4971

European Chemicals Agency (ECHA)
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/weight-of-evidence

Government of Canada
https://www.canada.ca/en/health-canada/services/chemical-substances/fact-sheets/application-weight-of-evidence-precaution-risk-assessments.html

https://www.canada.ca/en/environment-climate-change/services/canadian-environmental-protection-act-registry/related-documents.html

The French Agency for Food, Environmental and Occupational Health and Safety (ANSES)
https://www.anses.fr/fr/system/files/AUTRE2015SA0089EN.pdf

Martin et al. (2018)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6108859/pdf/EHP3067.pdf

Suter et al. (2017)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5726519/pdf/nihms919053.pdf
https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=NCEA&dirEntryId=338233

41. The before mentioned frameworks and publications apply several scoring systems in their assessments, yet they seemingly come down to two main methods, with and without quantitative scoring. For quantitative scoring, most notable the Klimisch score for toxicological data and the Bradford Hill criteria for epidemiological data are applied. The software-based Toxicological data Reliability Assessment Toll (ToxRTool) utilises the Klimisch categories to evaluate *in vivo* and *in vitro* data and provide comprehensive guidance on the quality of toxicological data. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach is one of the most widely used frameworks, originally addressing shortcomings of the grading systems in health care. The SEES report discusses both, the WoE approach and numerical scoring tools.

42. The links to the respective scoring systems and websites can be found below:

Klimisch score
https://www.sciencedirect.com/science/article/pii/S0273230096910764?via%3Dihub

Hill criteria
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1898525/pdf/procrsmed00196-0010.pdf

ToxRTool
https://ec.europa.eu/jrc/en/scientific-tool/toxrtool-toxicological-data-reliability-assessment-tool

GRADE
http://www.gradeworkinggroup.org/

43. While numerous papers, guidance documents and frameworks are available, there seems to be a lack of clear guidance on how to perform WoE evaluations in chemical risk assessment and how to apply the various scoring systems in a consistent manner.

44. The view of the Committee is sought, if this is an aspect the working group should address. The members are further asked to consider if separate conclusions should be drawn on the WoE approach or if the Committee would only like to discuss the WoE approach in regards to the integration of epidemiological and toxicological data.

Chapter 3

Application of approaches for dose response modelling.

45. Benchmark dose (BMD) modelling is used as a scientifically improved method for derivation of a reference point compared to use of the no observed adverse effect level (NOAEL). It also allows quantification of the dose response data uncertainty. The BMD methodology is now routinely used by EFSA and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in their chemical risk assessments and both have published guidance for its use by their Committees.

46. There are 2 software packages that are commonly used for BMD analysis. These are the BMDS developed by the US EPA and PROAST developed by the Dutch National Institute for Public Health and the Environment (RIVM) (an online version of the latter has been made available by EFSA).

47. EFSA Scientific Committee first issued guidance on use of the BMD approach in 2009. This has been superseded by their most recent guidance (EFSA, 2017). The main changes highlighted in the updated document include the preference for using model averaging (although it was acknowledged that at the time of publication this area is still under development); the use of Akaike Criterion Information to characterise the model goodness of fit to the data; addition of a flow chart to assist in how to perform BMD analysis; a template has been added to allow the analysis to be reported in a clear and transparent manner; and the preferred option is for the BMD confidence interval, rather than the BMD value to be reported. (EFSA, 2017).

48. A link to the EFSA guidance can be found here:

https://www.efsa.europa.eu/en/efsajournal/pub/4658

49. Early guidance on dose-response modelling published by the Food and Agricultural Organisation/World Health Organisation (FAO/WHO) was EHC 239 (FAO/WHO, 2009), which followed a workshop held in 2004. JECFA used the

outcomes of this workshop, alongside other developments to carry out dose-response modelling to calculate the margin of exposures (MOEs) for 6 genotoxic carcinogens (FAO/WHO, 2006). This approach was reassessed through use in further chemical evaluations in 2 subsequent publications in 2011 (FAO/WHO, 2011) and 2017 (FAO/WHO, 2017).

50. Links to these documents can be found here:

Environmental Health Criteria 239 (FAO/WHO, 2009)
http://www.inchem.org/documents/ehc/ehc/ehc239.pdf

Sixty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives (FAO/WHO, 2006)
https://apps.who.int/iris/bitstream/handle/10665/43258/WHO_TRS_930_eng.pdf;jsessionid=3C5A03E27239A890588776B0190B641A?sequence=1

Seventy-second report of the Joint FAO/WHO Expert Committee on Food Additives (FAO/WHO, 2011)
https://apps.who.int/iris/bitstream/handle/10665/44514/WHO_TRS_959_eng.pdf?sequence=1

Eighty-third report of the Joint FAO/WHO Expert Committee on Food Additives (FAO/WHO, 2017)
https://apps.who.int/iris/bitstream/handle/10665/254893/9789241210027-eng.pdf?sequence=1

51. The US EPA produced a “Benchmark Dose Technical Guidance” document (US EPA, 2012) which provides general guidance on BMD modelling, which can be applied to software packages other than BMDS (US EPA’s BMD modelling software) and other dose response models. The EPA presented at EuroTox 2018 and highlighted the BMD processes used by both EFSA and the US EPA. The presentation (US EPA, 2018) also highlighted areas of harmonisation between EFSA and the EPA.

52. Links to these documents can be found here:

Benchmark Dose Technical Guidance (US EPA, 2012)
https://www.epa.gov/risk/benchmark-dose-technical-guidance

EPA and EFSA Benchmark Dose Guidance (US EPA, 2018)
https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=341863&Lab=NCEA

53. A review of BMD modelling from 2018 can be found here:

https://www.ncbi.nlm.nih.gov/pubmed/29516780

Chapter 4

Uncertainty analysis, weight of evidence and risk prioritisation tools

54. The proposed guidance document/framework will need to consider the uncertainties in the overall risk assessment and/or the exposure considerations in both types of studies, toxicological and epidemiological, describing the strength and weaknesses of both types of studies and the assumptions and extrapolations made to come to an overall conclusion. Depending on the approach taken, the uncertainties can either be included in each Chapter or it might be feasible to summarise the uncertainty in a separate Chapter as currently proposed, giving emphasis to uncertainties in the WoE and BMD modelling.

55. The consideration of weight of evidence and uncertainty will also consider the use of risk prioritisation tools. This will include a review of the range of tools available, analysis of their strengths and weaknesses and their appropriateness for toxicological and epidemiological data.

56. Some guidance documents on uncertainty in risk assessment are available from the COT and other regulatory agencies and the links can be found below.

COT
https://cot.food.gov.uk/sites/default/files/cot/vutreportmarch2007.pdf

EFSA
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5123

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5520

WHO/IPCS
https://apps.who.int/iris/bitstream/handle/10665/259858/9789241513548-eng.pdf;jsessionid=E17B6C15B964AE0FD308F2E02D99F21C?sequence=1

Chapter 5

Discussion, conclusions and recommendations

57. This will take into account the discussions of the working group, including conclusions and recommendations by the working group and subsequently the Committee.

Literature search

58. Most international guidance documents and frameworks focus on specific endpoints or chemicals, a systematic literature search has not been performed to date. Documents given above have been retrieved through a brief initial literature search, without systematically applied search terms.

59. The following search engines and search terms are proposed for a systematic literature review. The Committees knowledge and comments are sought on the proposed.

Search engines

60. Several search engines are being considered, some of which have been previously applied by the Secretariat, others have been applied by the frameworks given above.

- PubMed
- ToxNet (Toxline)
- MedLine (MeSH terms)
- Embase (EMTREE)
- Science Direct
- Cochrane
- Google Scholar

61. Following the systematic approach and approaches by other agencies, the use of screening tools such as EFSAs Shiny R and Distiller are furthermore being considered.

Search terms

62. The following search terms are proposed by the Secretariat for subsequent literature searches. Considering the various aspects of the proposed work scope, the search terms have been split by the proposed chapters/information to be included.

Integration epidemiological and toxicological evidence/data (Chapter 1)

> (epidemiological AND toxicological) AND (integrated OR synthesising OR combined OR systematic OR causal OR association OR quantitative OR evidence integration OR evidence based OR weight of evidence OR WoE)

Weight of evidence (Chapter 2)

> (epidemiological OR toxicological) AND (weight of evidence OR WoE OR Klimisch OR Hill OR PECO)

Application of approaches for dose response modelling (Chapter 3)

> (epidemiological AND toxicological) AND (BMD OR BMDL OR benchmark dose OR benchmark dose modelling OR POD OR point of departure)

(epidemiological OR toxicological) AND (BMD OR BMDL OR benchmark dose OR benchmark dose modelling OR POD OR point of departure) AND (integrated approach OR integrated data OR evidence integration OR weight of evidence OR WoE)

(BMD OR BMDL OR benchmark dose OR benchmark dose modelling) AND (integrated approach OR integrated data OR evidence integration OR weight of evidence OR WoE)

Uncertainty analysis (Chapter 4)

(uncertainty OR uncertainty analysis OR uncertainty assessment) AND (integrated OR synthesising OR combined OR systematic OR causal OR association OR quantitative OR evidence integration OR evidence based OR weight of evidence OR WoE)

Questions to the Committee

i) Does the Committee agree that it would be useful to form a joint working group (with COT) provide guidance on the integration of epidemiological and toxicological data? If not, how would the Committee suggest taking this forward?

ii) What form of output would the Committee consider useful from the formation of a sub-group?

iii) Does the Committee have any proposal for the Terms of reference for the WG including an appropriate and realistic time scale for the work?

iv) Would the Committee also like separate conclusions to be drawn on the WoE and BMD approaches?

v) Would the Committee also deem it appropriate to get COM and COMEAP input on the term of references and proposed work scope?

vi) What expertise would the Committee consider necessary for the sub-group? Do members have specific experts in mind?

vii) What initial work would the Committee/Members require from the Secretariat before the first meeting, for example regarding literature searches and summaries (based on these requirements the Secretariat will propose dates for this meeting)?

viii) The Committees comments and knowledge are sought on the proposed search engines and search terms for a systematic literature search.

ix) Do the members have any other comments?

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Secretariat
July 2019