Meeting

Monday 22nd of June 2020

Fourth meeting of the COT and COC SETE subgroup

COT and COC subgroup on the synthesis and integration of epidemiological and toxicological evidence (SETE) in risk assessments

Agenda

Agenda of the third Meeting, Monday 22nd of June 2020, 12:30 to 3:30 pm, via teleconference

1. Welcome and goals of meeting
2. Discussion of the outcome from the epidemiological subgroup
3. Discussion of the outcome from the toxicological subgroup
4. Next steps

   Integration of epidemiological and toxicological evidence
   Drafting of text for guidance document and report
5. Administrative: update on SETE website and plan next meeting(s)

Minutes

Present:

Chair: Alan Boobis

Committee Members:

- Phil Botham
- Gill Clare
- Gunter Kuhnle
- George Loizou
- David Lovell
- Neil Pearce
- Lesley Rushton

- Mireille Toledano
- Heather Wallace
- Alison Gowers, PHE
- Valentina Guercio, PHE

Secretariat:

- Barbara Doerr, FSA
- Cath Mulholland, FSA
- Britta Gadeberg, PHE

The Chair welcomed Members and other attendees.

Prof Gunter Kuhnle introduced the work of the epidemiological subgroup. A lot of valuable information has previously been published, such as the Bradford Hill considerations and the SEES report. The epidemiological subgroup agreed with the SEES report, that it was not appropriate to apply a tick box approach to quality rating of studies, but that all the evidence would need to be considered and assessed. Members felt that the best way to do so would be a transparent approach documenting the biases, weaknesses and strengths of individual studies and to evaluate them as a whole. Members of the WG noted that this approach was similar to EFSAs uncertainty approach but pointed out that some studies are quite complex (environmental contaminants, sources in food) and it can therefore become complicated when biases work/pull in different directions.

Members noted that there are uncertainties surrounding occupational studies due to the relatively small numbers of participants and the need to extrapolate to the general population as well as biases around the publishing/reporting of negative data. Some methods of visualising or assessing publication bias and lack of negative data are available, such as meta-analysis or funnel plots which can provide an indication of where data are missing or in which direction data are weighing.

One of the more general issues raised by the epidemiological subgroup was the fact that it is often difficult to integrate epidemiological data/studies with toxicological information as the information provided from epidemiological studies is often not usable for toxicology. Members agreed in an ideal scenario, discussion about e.g. endpoints, exposure, mode of action, would happen at the start of an epidemiological study in conjunction with toxicology colleagues. In reality, exposures from epidemiological studies are often not relevant/informative to the problem being addressed. It is therefore important to acknowledge the

limitation of these studies yet make the most of the information available.

Members agreed that it would be useful to have discussions throughout the assessment about the obvious differences and to continue the dialogue about what information would be useful and supportive of the overall question being addressed.

Dr Phil Botham introduced the work of the toxicological subgroup. As with the epidemiological evidence stream, there was a lot of work done on the assessment of toxicological studies prior to this. The Members of the subgroup pointed out four papers that they felt were the most relevant and to which they would be referring. These included a number of checklists as to which questions to be asked to assess the quality of a study. However, as with the epidemiological subgroup, Members did not feel comfortable with the idea of a check list or tick box approach as it would take away expert judgement. The Members tried to provide a more general approach about what questions should be considered and which questions would help to provide transparent expert judgement.

Rather than applying a checklist approach, all Members were in favour of using expert judgement in a transparent way. Compliance with OECD guidelines and GLP are a good indication of the reliability of studies, however Members pointed out that while a study can be of good quality, the key information to a certain question can still be missing. Therefore, for studies which deviated from guidelines, it should be noted how they deviate and if or how this deviation affects interpretation as they may still be good quality and useful studies. Members also noted the problem surrounding data transparency (access to raw data) and replication and consistency in studies.

Members stressed that it was important to have a continued conversation between toxicological and epidemiological assessors/experts to ensure that the right questions were being asked and the endpoints and approaches were aligned. Members agreed that problem formulation was key to determine the information that would be helpful for a specific assessment and to include and stress this at the start of the guidance document. In doing so, it would not be a decision on good or bad studies but a transparent approach to decide which studies would be the critical ones and why these studies have been selected. Members stressed that transparency was key.

Following the discussions minuted above, the respective sub-groups will continue to draft their sections and also include information on exposure and criteria on how to assess the quality of exposure data, as Members felt this was a vital part

to the overall assessment.

Members were still in agreement that the overall approach taken by the Epid-Tox framework using the two evidence streams to weaken or strengthen the causal relationship was appropriate. Therefore, the subgroup on scaling evidence will provide a first draft at the next meeting

The mode of action (MoA) was a key element in the Epid-Tox framework to link toxicological, epidemiological and exposure information and to strengthen causality and plausibility of effects. Members agreed that it would be useful to include a section on MoA in the guidance document and a first draft will be provided by the Chair for the next meeting.

The Secretariat will further provide a draft outline for the SETE report, using the SEES report for guidance.

The next meeting will be held on in early September 2020, via TC.