Meeting

Monday 21st of September 2020: SETE meeting

Fifth 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 fifth Meeting, Monday 21st of September 2020, 10:00 am to 1:00 pm, via teleconference

1. Welcome and goals of meeting
2. Update on the work of the epidemiological and toxicological subgroup
3. Discussion of the outcome from the scaling of evidence subgroup; the WG input is especially sought on the scales/definition of the relationship grid and examples
4. Discussion of the section on Mode of Action
5. Discussion of the section on problem formulation, literature retrieval and general outline of the report.
6. Next steps: drafting of text for guidance document and report
7. Administrative: update on COT/SETE website, TEAMs, plan next meeting(s)

Minutes

Present

Chair: Alan Boobis

Committee Members:

- Phil Botham
- Gill Clare
- Alison Gowers

- Gunter Kuhnle
- George Loizou
- David Lovell
- Mireille Toledano
- Heather Wallace

Secretariat:

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

Apologies were received from Lesley Rushton, Neil Pearce and Valentina Guercio.

The Chair welcomed Members and other attendees.

The general structure of the report was endorsed by all Members. For the next meeting Members were asked to consider the information to include in the guidance document, which should be a pragmatic and shorter version of the report. The Secretariat was asked to provide headings and brief information based on the SEES guidance for the next meeting to facilitate discussion.

Members raised the importance of ensuring that the SETE guidance is applied appropriately and suggested that additional text be added to the section on problem formulation, including considerations on exposure scenarios and the importance of identifying populations of potential concern. Members further concluded that the section needs to reflect more broadly the questions the Committees are asked to assess and suggested that the section on problem formulation is linked with the section on literature retrieval. Independent of a systematic literature review being required, the literature search may not necessarily focus on one end point but could include or focus on other aspects, such as a population or specific chemical of concern. Members asked for the Secretariat to link to the SEES report, where appropriate.

Prof Gunter Kuhnle provided an update on the work of the epidemiology subgroup. The main point emphasised by the subgroup was that the bias as well as the strength and weaknesses of each study should be assessed, rather than simply using a scoring system. In rating the overall body of evidence, the subgroup favoured a flexible approach to combine all studies and considered triangulation to be the most suitable approach. Members raised concerns about including all studies available, regardless of quality, but noted that no one

method was suitable for all approaches and that expert judgment was required to determine which method is most appropriate for which assessment. Members suggested it may be useful to work through an example or provide examples of different cases and which methods of assessment may be the most appropriate or as an alternative to provide a set of criteria/questions/indications how best to approach this issue. Members concluded that it would be useful to reflect these discussions in the SETE guidance document and stressed the importance of understanding the uncertainties and limitations. Where possible, the document should refer to the SEES report, as several aspects would/should have been addressed in that report already.

Dr Phil Botham provided an update on the work of the toxicology subgroup. The work built on the previous document and additional information had been added on how to assess non GLP studies and exposure. Members asked for the text on the use of *in vitro* studies to be expanded and to include information regarding method validation/verification for non-OECD *in vitro* studies, mainly how and to which degree such studies would be assessed and the influence they may have on the overall assessment/integration of the data. Members were informed by the subgroup that the Kaltenhouser/Goodman paper provided tables with relevant information and Members agreed that where suitable, rather than reproducing identical questions, previous guidance would be endorsed by the working group and referred to in the SETE document.

Following the update by the toxicology subgroup, Members discussed the issues around exposure in detail and recognised that this aspect would require further work. For a risk from dietary exposure, other than for local effects, the chemical would need to be absorbed (in humans), if this is not the case then effects from systemic exposure (in animals) would not be informative. However, (systemic/experimental) exposure can play a role in defining the endpoint, if no systemic exposure occurs then the study itself would not usually be helpful. Members acknowledged the differences between exposure in animal/experimental and epidemiological studies, the latter often providing information on a general association rather than a specific hazard identification. The assessment of an effect from epidemiological data is often done on the totality of the database, not on individual studies. Members agreed that the first step in the integration process is the question whether or not the exposure to a substance causes an effect in humans and noted that it is often difficult to provide a clear answer. Members therefore concluded it would be useful to have a separate section on exposure in the SETE document and some Members volunteered to provide a first draft for the next meeting.

Prof Alan Boobis provided an introduction to the section on mode of action (MOA) and emphasised that the MOA and its key events provide a useful and powerful bridge between experimental studies (animal, *in vitro*, *in silico*) and observations in human populations. Identification of an MOA for an adverse effect in experimental animals that is considered relevant to humans would add appreciable evidence of causality to an association observed in humans. Members were asked to what extent the group would agree with the more quantitative approach taken in the Negri et al. paper on PFAS, which included PBPK modelling and mode of action considerations. Members discussed the possibility of a more quantitative approach in the guidance document and concluded that while there are quantitative considerations in the current framework, anything further is outside the scope of this working group. Members acknowledged differences in opinion among experts on the relative importance of mechanistic and empirical data, however in principle the SACs utilise a mechanistic approach to the extent possible. Members agreed that the section would benefit from additional text covering the discussion and points raised.

The Secretariat provided an introduction to the section on scaling and integration of evidence, briefly outlining the more general considerations and questions that had been raised in the subgroup meeting regarding the criteria/scales of the causality grid and practical examples to consider. Members noted that the tabular presentation of the weighing of evidence was the important aspect of this section, once conclusions on the influence of the separate evidence streams had been drawn it was simply a matter of displaying said conclusions. Members acknowledged that the caffeine example and general considerations presented were drawing on previous work on uncertainties and would require a clearer separation of qualitative and quantitative information for the work undertaken here.

Members agreed that it would be useful to test the guidance document/framework produced by the Working Group on a complex example.

COT has recently decided to (re-)assess dioxins, and Members of the Working Group thought it could be a good and complex example to test the applicability of the framework. However, Members acknowledged that the assessment on dioxins would take extensive work and time and agreed that it would be useful to publish the first iteration of their framework prior to when the work on dioxins may be completed. Members agreed to initially apply/test the practicality of the suggested guidance on tropane alkaloids and hence adjust the integration of epidemiological and toxicological data, if necessary. The Working Group would

then publish an interim/draft guidance/framework, which in turn, if COT and COC agree, would be put to a practical and complex test on dioxins later in 2021.

The next meeting will be held on 16th November 2020, via TC.