Report of the Synthesis and Integration of Epidemiological and Toxicological Evidence Subgroup (SETE) of the Committee on Toxicity and the Committee on Carcinogenicity – Lay summary

The UK Committees on Toxicity (COT) and on Carcinogenicity (COC) regularly review epidemiological and toxicological evidence in their risk assessments. There is, therefore, a need for guidance on the approaches used by the Committees to integrate these evidence streams, both for scientific consistency and to ensure public transparency. To that end, the Committees established the Synthesising and Integration of Epidemiological and Toxicological Evidence Subgroup (SETE) to review and document current practice and provide applicable guidance.

SETE recognised that issues on which advice from the Committees is sought varies considerably and hence the guidance proposed should be sufficiently flexible to address this.

Scoping and problem formulation were identified as the crucial first step in the process. This ensures the right questions are asked, helps make the most efficient use of resources and identifies the most appropriate approaches to use in the assessment. An established system or guidance to assess the separate/different evidence streams should be followed where feasible.

For both epidemiological and toxicological evidence, a prescriptive checklist or scoring approach is not recommended. However, identifying the strengths and weaknesses of studies is important. The decision-making process should be robust, transparent, evidence-based, defensible and documented, but equally importantly, it should be easy to use. Collaboration and ongoing dialogue between epidemiologists, exposure experts and toxicologists are strongly advised. Information on mode of action (MOA) can be invaluable for evidence integration as it underpins weight of evidence considerations by providing the mechanistic link between empirical observation and biological plausibility.

All lines of evidence should be considered, with no pre-existing hierarchy. One way to clearly depict the influence of the different lines of evidence on causality is via visual representation (Figure 1).

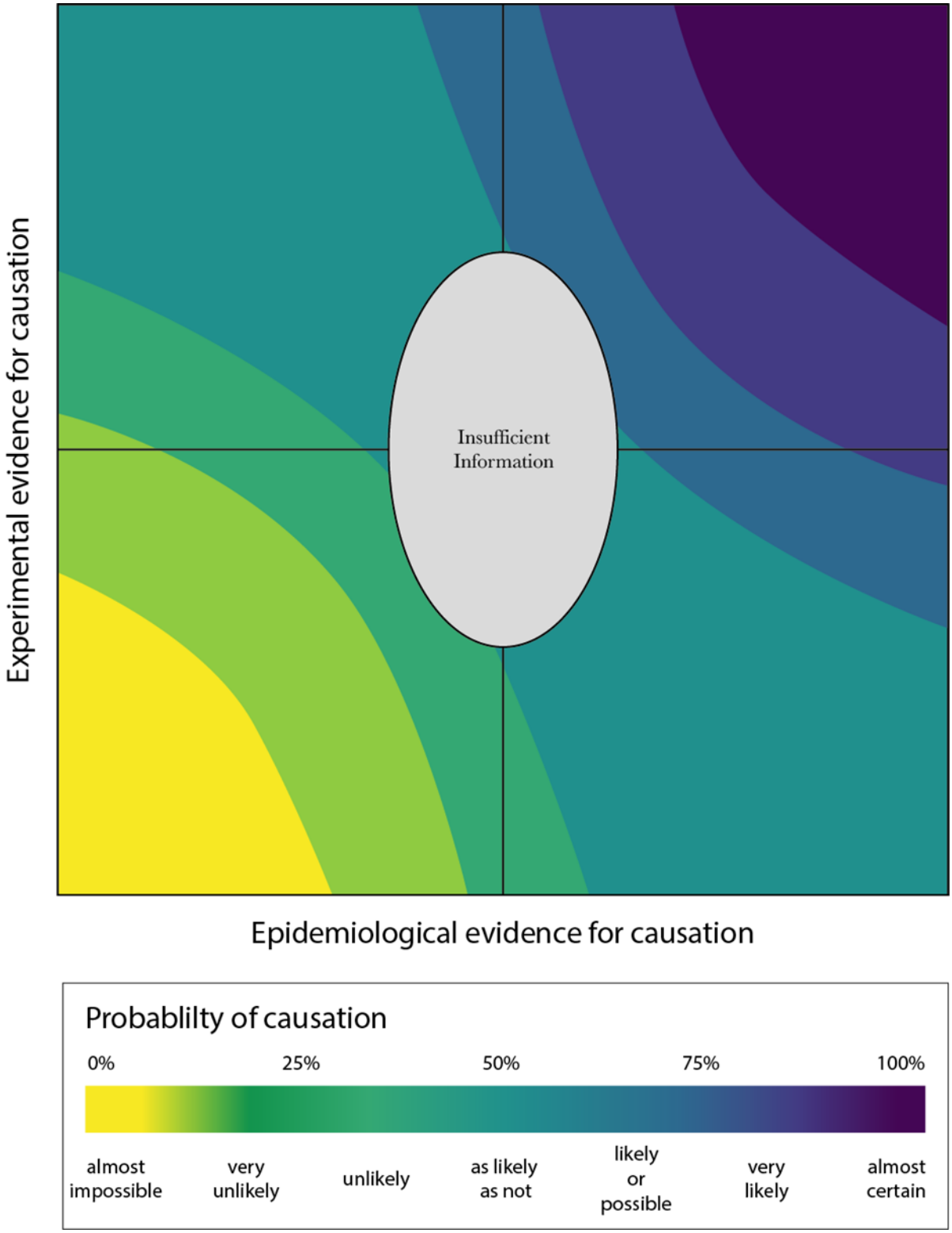

Figure 5: Example for the visual representation of the likelihood of a causal relationship, considering both epidemiological and toxicological data.

Decisions on whether there is sufficient information to reach a conclusion or whether a causal relationship in humans is more likely or unlikely can be reached based on where the causal relationship appears on a graph. It is important to begin with the initial estimate of causal relationship at the centre of the graph. Depending on

whether the toxicological, mechanistic or epidemiological evidence assessed supports or discounts (or has no clear influence on) a conclusion of causality, placement on the graph is then moved accordingly, either in a positive or negative direction. The movement is influenced by several factors, including the strength or weakness of the evidence, any relative weighing given to epidemiological and toxicological studies and the uncertainties associated with the data. As more information is included in the process and/or becomes available, the placement of the toxicological and/or epidemiological evidence can be easily adjusted and the impact on any possible conclusion easily seen.

In contrast to other approaches, the above visualisation aims to provide a pictorial representation of the consensus views of a Committee on the influence of the different lines of evidence on causation, assessed by debate and agreement of scientific experts. In this way, it provides a more objective means of collating the views of the Committee and communicating the agreed conclusion of a Committee on the likelihood of causation.

The conclusion should be stated, with an estimate of the overall uncertainty and, where appropriate, guidance on how data gaps could be filled.

The full SETE report and guidance document (Annex 1) can be found Link to report and annex.

Please note, the guidance will be trialled by the COT for 2 years and then reviewed.