Synthesis and Integration of Epidemiological and Toxicological Evidence (SETE)

Dr Barbara Doerr, UK Food Standards Agency

Prof Alan R Boobis, Imperial College London

Slides: Dr Philip A Botham, Syngenta

Background

- UK science advisory committees (SACs) provide independent advice to government departments and agencies

  Committee on Toxicity of chemicals in food, consumer products and the environment (COT) provides advice on the toxicity of chemicals – principally to the Food Standards Agency (FSA)

  Committee on Carcinogenicity (COC) provides advice on the carcinogenicity of chemicals used in pesticides, pharmaceuticals and other products

- In 2018, COT and COC published a report from its Synthesising Epidemiological Evidence Sub-group (SEES)

- In 2019, the Committees recognised the need for parallel guidance on toxicological evidence and on the integration of the different evidence streams in a systematic and transparent manner and established the Synthesis and Integration of Epidemiological and Toxicological Evidence (SETE) sub-group

Objectives

- Review the guidance on assessing epidemiological evidence
- Provide guidance on assessing toxicological evidence
- Review recent practices and frameworks on combining epidemiological and toxicological evidence, with a focus on integrating the two evidence streams
- Develop pragmatic guidance on how different evidence streams should be integrated in a transparent manner, giving appropriate weight to all
- The focus thereby was to integrate evidence to conclude on the plausibility and causality of an effect

Recent approaches to integration

- Epid-Tox Process Adami H-O, Berry CL, Breckenridge CB, Smith LL, Swenberg JA, Trichopoulos D, Weiss NS, Pastoor TP (2011). Toxicology and epidemiology: Improving the science with a framework for combining toxicological and epidemiological evidence to establish causal interference. Toxicological Science, 122(2): 223-34.
- ECETOC Lavelle KS, Schnatter AR, Travis KZ, Swaen GMH, Pallapies D, Money C, Priem P, Vrijhof H (2012). Framework for integrating human and animal data in chemical risk assessment. Regulatory Toxicology and Pharmacology. 62: 302-12.
- WHO/IPCS Mode of Action/Human Relevance Framework Meek ME, Boobis A, Cote I, Dellarco V, Fotakis G, Munn S, Seed J, Vickers C (2014). New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. Journal of Applied Toxicology, 34(1): p 1-18
- EFSA (2017). EFSA Scientific Colloquium 23 – Joint European Food Safety Authority and Evidence-Based Toxicology Collaboration Colloquium Evidence integration in risk assessment: the science of combining apples and oranges.
- US-EPA Integrated Risk Information System (IRIS) for risk hazard assessment approaches for environmental contaminants. https://www.epa.gov/iris
- OECD uses the Integrated Approaches to Testing and Assessment (IATA) to support chemical safety. https://www.oecd.org/chemicalsafety/risk-assessment/iata /

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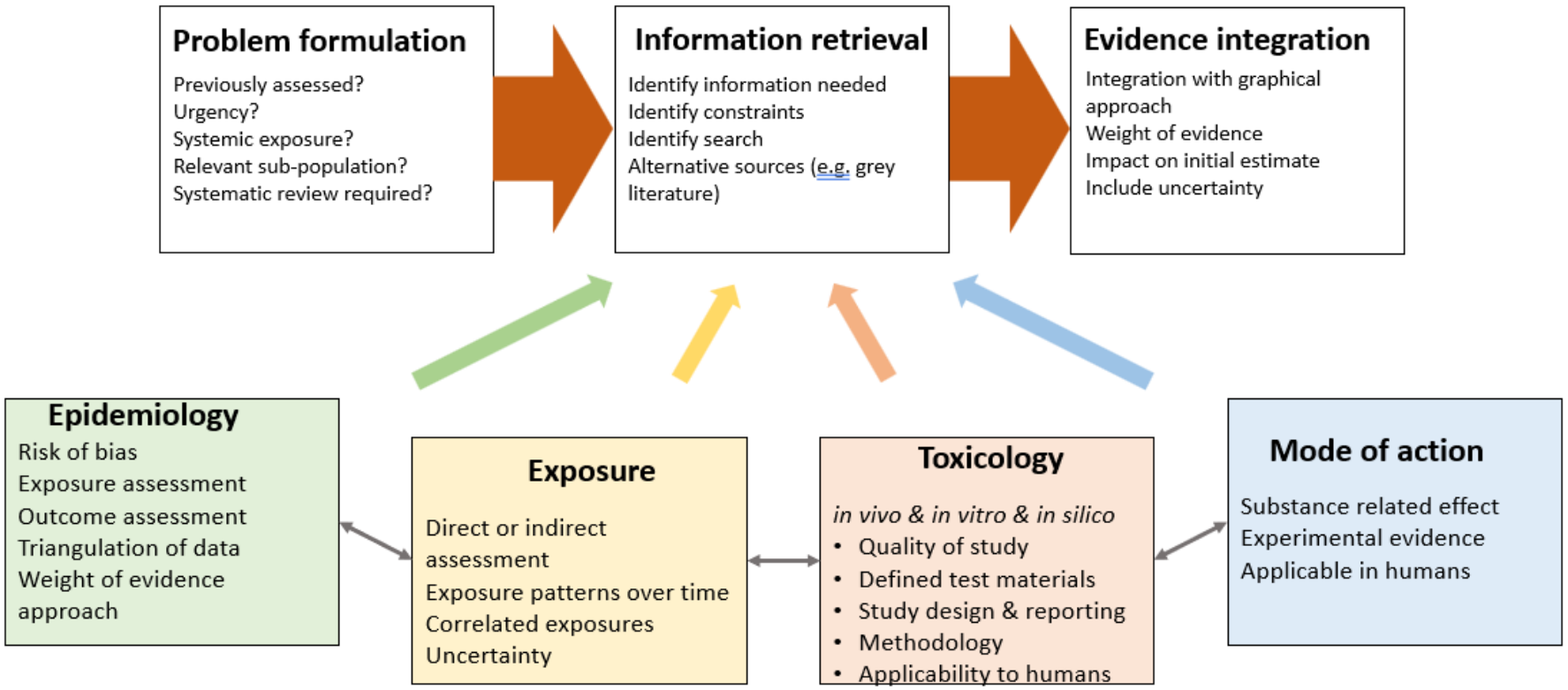
Overview of the SETE approach



Scope/Problem formulation

- Ensures the right questions are asked, e.g. why is a review needed, population of concern, exposure pathways, qualitative (e.g. causation) or quantitative (e.g. safe level) conclusion, exposure sources
- Ensures the most efficient use of resources
- Identifies best approach to use for specific assessment
- Developed by risk manager in discussion with the committee/risk assessor

Literature/Information retrieval

- Is a systematic review required?
- Has the issue been addressed recently by another authoritative body? How up-to-date are previous evaluations?
- What information is being sought?

Urgency of request may influence the scope of information retrieval

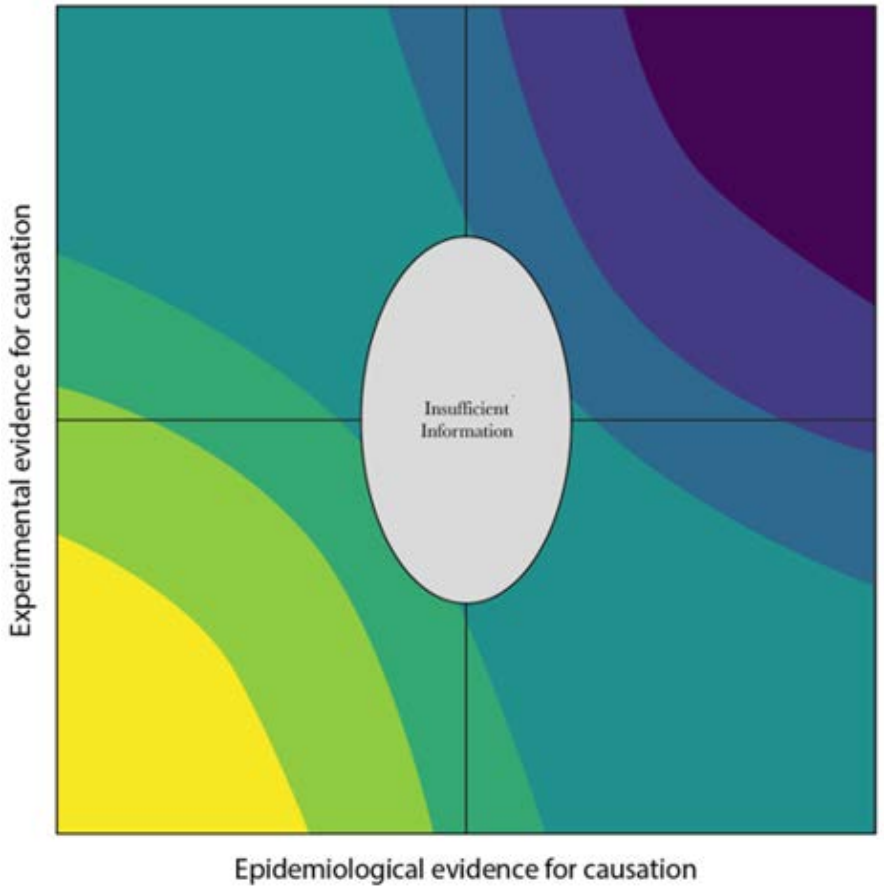
Evidence integration

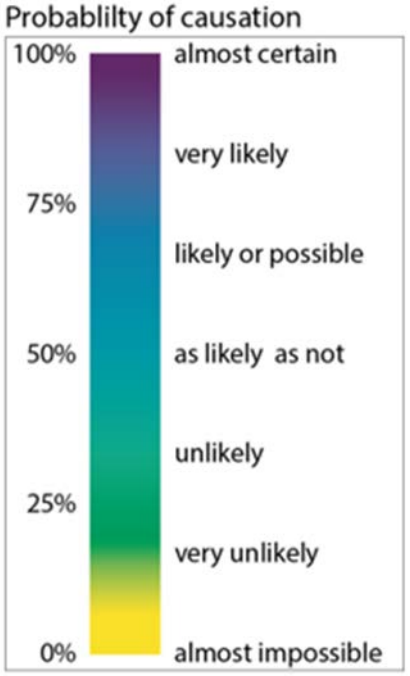
- How strong is the epidemiological evidence that exposure causes an adverse effect in humans
- How strong is the evidence that exposure causes an adverse outcome in experimental studies and is the observed outcome relevant to humans
- Are the exposures realistically achievable in the population of concern (concentration, duration)
- Is there sufficient information to establish a mode of action (MOA); is there evidence from other information/evidence streams (e.g. in silico, NAMs) that key events will lead to adverse outcomes in humans

Key Additional Step - Visualisation

- Encourages and assists discussion of final conclusion
- Provides clear depiction of the influence of the different lines of evidence on the null hypothesis of causality
- Communicates clearly whether there is sufficient information to reach a conclusion on the likelihood of a causal relationship in humans
    - Is a causal relationship in humans more likely or less unlikely
- Reflects and communicates the outcome of a deliberative, weight of evidence approach, taking account of uncertainties in the assessment
- Should be accompanied by a transparent narrative description or tabulation of the information/discussion and decision making

Visualisation





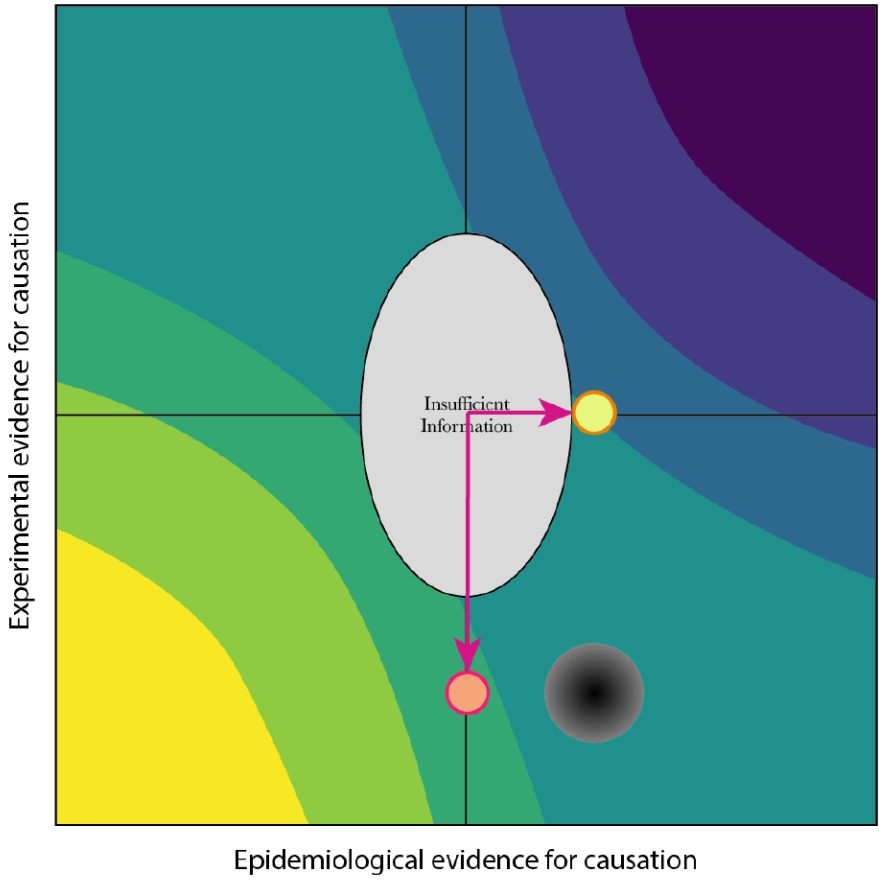
Pictorial representation of the consensus view; not a probabilistic or numerical approach

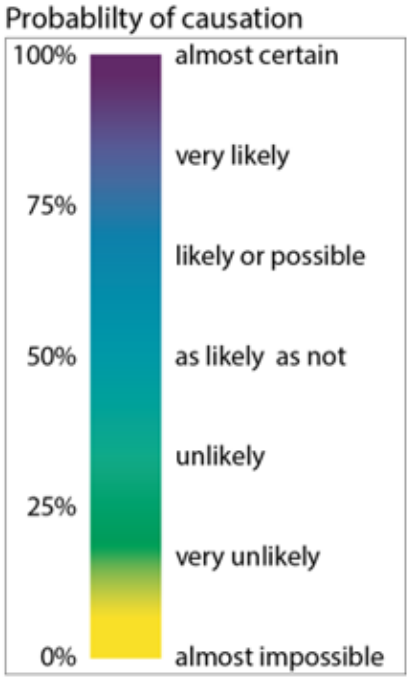
Adapted from Adami et al. (2011)

Example: Caffeine and developmental toxicity

Line of evidence	Influence on conclusion
Animal data: Effects seen at maternally toxic doses	Uninformative
Human data: Evidence for effect on fetal growth restriction in high quality intervention and cohort studies Uncertainties in exposure assessment, residual confounding, study design	Evidence for an effect but unclear whether it is causal
Mechanistic data: No mechanism could be identified for effect on FGR	Uninformative

Example: Caffeine and developmental toxicity





A causal relationship between caffeine intake and increase in FGR is possible but lacks experimental support

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Example: Tropane alkaloids and neurotoxicity

Line of evidence	**Influence on conclusion**
Animal data: Clear anticholinergic effects	Evidence for causal effect
Human data: Observational and clinical studies show effect, but some uncertainties in exposed population (dose-response, nature of exposure)	Although there are some uncertainties, evidence supports causality
Mechanistic data: Clear mechanistic understanding for effect	Strong evidence for causal effect

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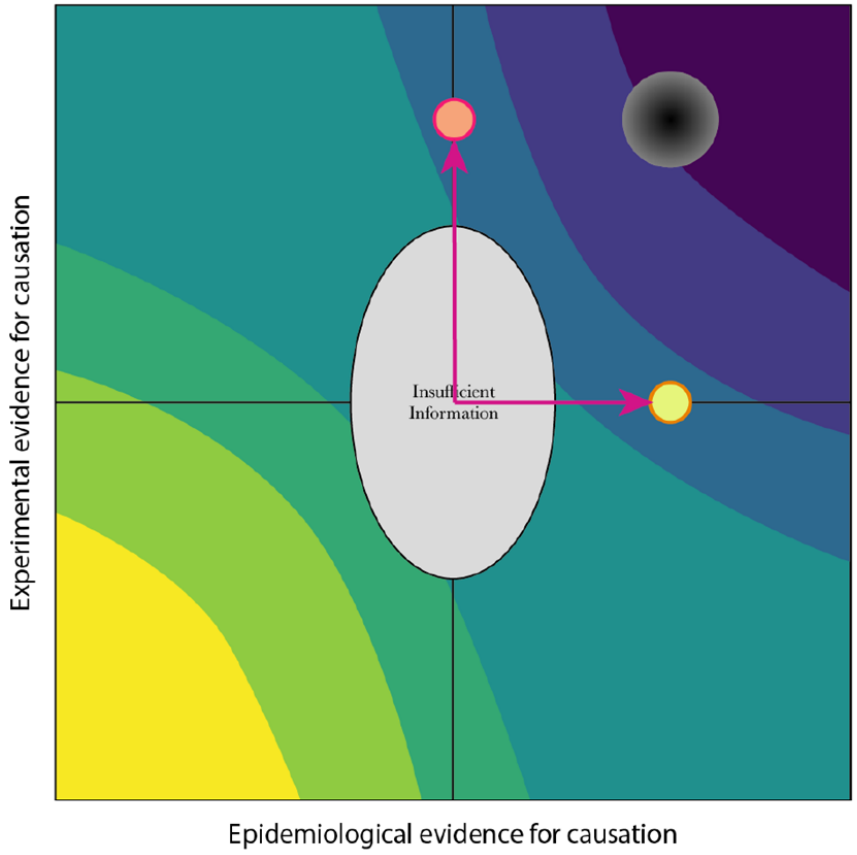
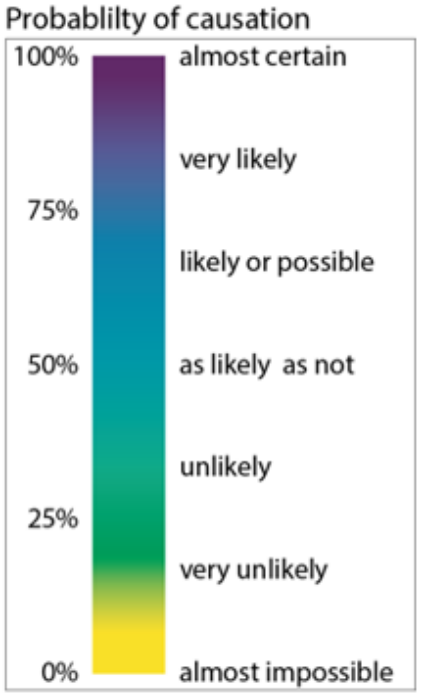
Example: Tropane alkaloids and neurotoxicity



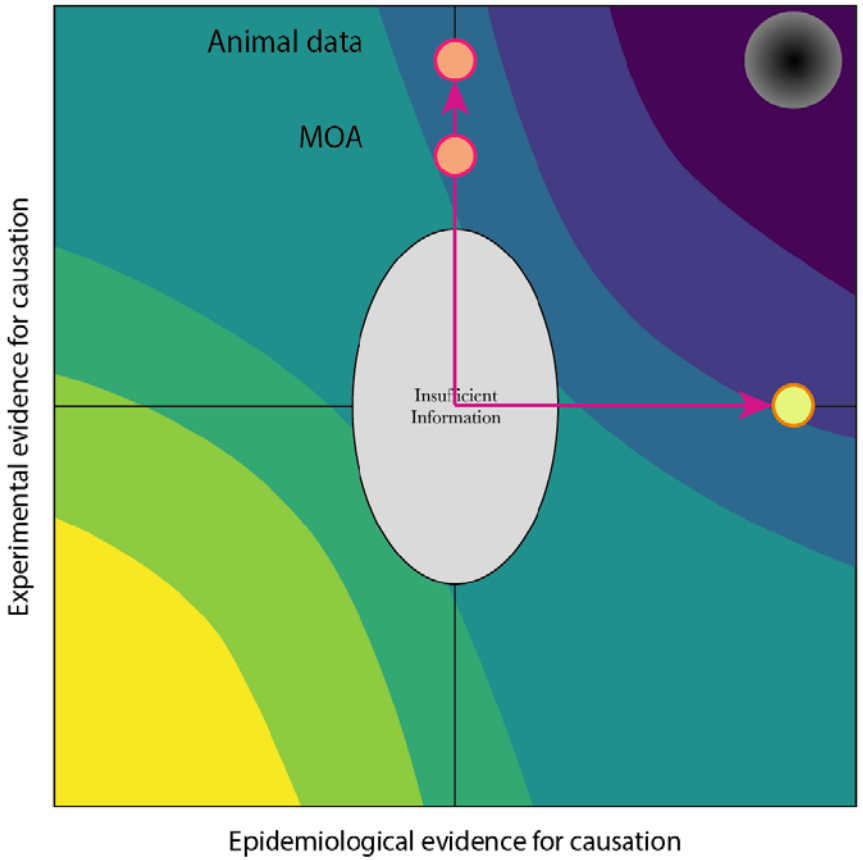


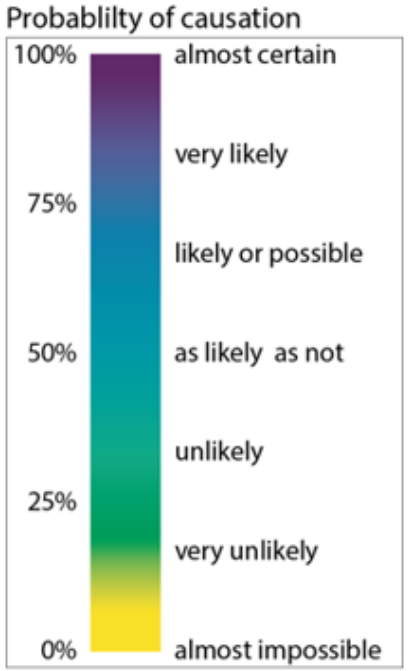
A causal relationship between TAs, in this case hyoscyamine/atropine and scopolamine, and anticholinergic effects from dietary sources is likely

Example: Cadmium and nephrotoxicity

Line of evidence	Influence on conclusion
Animal data: Target organ specificity, with clear effect on kidney	Evidence for causal effect
Human data: Consistent evidence from range of study designs for effects on kidneys. Dose response relationship.	Strong evidence for causal effect
Mechanistic data: Mode of action well understood, with key event linkage in humans.	Strong evidence for causal effect

Example: Cadmium and nephrotoxicity





Epidemiological and experimental animal data provide strong evidence for a causal relationship between cadmium and renal toxicity.

This is further supported by the reported link between the MoA and human data.

Conclusion

- The components of the SETE guidance are not new (not the intention)
- It reflects current practice but provides a structured, transparent approach for its application
- The emphasis is on weight of evidence and evidence integration
- A visualisation tool has been suggested to help in communicating deliberative, consensus conclusions on the contribution of different lines of evidence and on an overall conclusion on causation
- The guidance should contribute to the consistency, transparency and communication of the work of the committees
- The guidance has potential wider applicability, for example in regulatory decision-making

Output

- Report of the Synthesis and Integration of Epidemiological and Toxicological Evidence Subgroup (SETE) of the Committee on Toxicity and the Committee on Carcinogenicity
- https://doi.org/10.46756/sci.fsa.sjm598

- Annex 1: Guidance of the Synthesis and Integration of Epidemiological and Toxicological Evidence Subgroup (SETE) of the Committee on Toxicity and the Committee on Carcinogenicity
- https://doi.org/10.46756/sci.fsa.sjm598

- 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
- https://cot.food.gov.uk/SETEworkinggroup

- **Peer-review publication in preparation**

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Thank you

Barbara.Doerr@food.gov.uk

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