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Title page

A UK Framework for the Assessment and Integration of Different Scientific Evidence Streams in Chemical Risk Assessment

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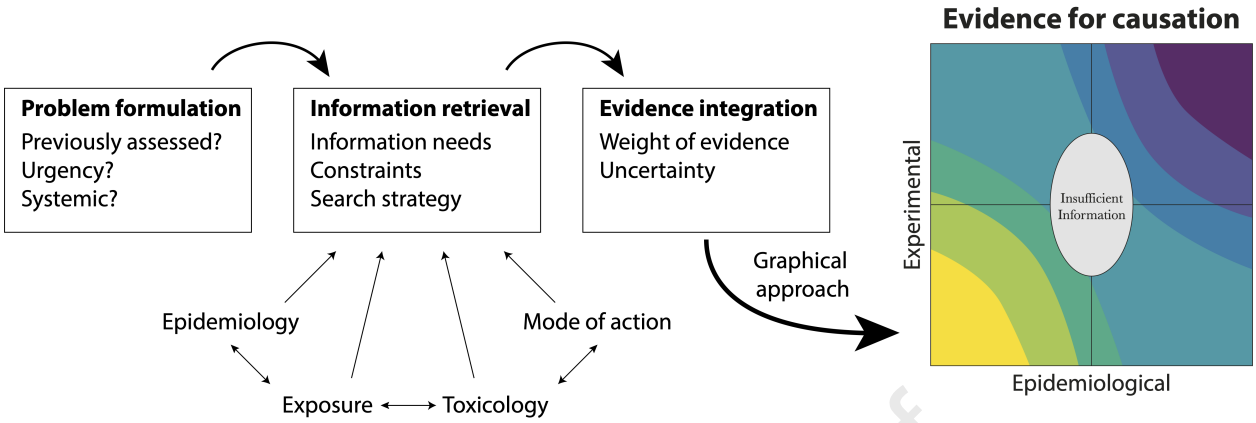
Abstract

Background: Few methods are available for transparently combining different evidence streams for chemical risk assessment to reach an integrated conclusion on the probability of causation. Hence, the UK Committees on Toxicity (COT) and on Carcinogenicity (COC) have reviewed current practice and developed guidance on how to achieve this in a transparent manner, using graphical visualisation.
Methods/Approach: All lines of evidence, including toxicological, epidemiological, new approach methodologies, and mode of action should be considered, taking account of their strengths/weaknesses in their relative weighting towards a conclusion on the probability of causation. A qualitative estimate of the probability of causation is plotted for each line of evidence and a combined estimate provided.
Discussion/Conclusions: Guidance is provided on integration of multiple lines of evidence for causation, based on current best practice. Qualitative estimates of probability for each line of evidence are plotted graphically. This ensures a deliberative, consensus conclusion on likelihood of causation is reached. It also ensures clear communication of the influence of the different lines of evidence on the overall conclusion on causality. Issues on which advice from the respective Committees is sought varies considerably, hence the guidance is designed to be sufficiently flexible to meet this need.

Synthesis and Integration of Epidemiological and Toxicological Evidence (SETE)



1. Introduction/Background

The assessment and integration of epidemiological, toxicological and other evidence streams for risk assessment purposes is an integral part of the work conducted by any scientific advisory committee (SAC). However, current approaches usually consider epidemiological evidence separately from toxicological evidence, and then combine the information at the end, most often in a non-systematic way. There are several methods available for quantitative synthesis of epidemiological studies (SEES, 2018; EFSA, 2020) but only a few methods exist for combining epidemiological and toxicological studies to reach an integrated conclusion in a transparent manner.

International bodies such as the International Programme of Chemical Safety (IPCS), the European Food Safety Authority (EFSA) together with the Evidence-Based Toxicology Collaboration (EBTC), the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT, Rooney et al. 2014), the International Agency for Research on Cancer (IARC), the US Environmental Protection Agency (EPA) and the Organisation for Economic Co-operation and Development (OECD) have published guidance or frameworks which focus on or include considerations on data integration in general, or for specific endpoints, e.g. carcinogenicity. Several papers have also been published on the integration of different evidence streams, focusing either on a general approach/framework (Adami et al, 2011; Lavelle et al., 2012) or specific endpoints (Boyes at al., 2005) or chemicals (Negri et al, 2017).

While all of the beforementioned frameworks and approaches have aspects or steps in common, e.g. problem formulation, (systematic) literature reviews, and quality

assessment of studies, there are only a small number that provide practical and applicable guidance on combining epidemiological and toxicological studies to reach a conclusion on causality and none of these fully reflect the approach by the UK SACs. Hence, in 2019, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) and the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) set up the Synthesis and Integration of Epidemiological and Toxicological Evidence Subgroup (SETE) to address this issue.

The aims of this paper are to briefly summarise the main considerations for the assessment of different evidence streams, to provide pragmatic guidance and transparent reflection on how the UK SACs review data, how different evidence streams should be integrated in a transparent manner, giving appropriate weight to all, and using graphical visualisation to ensure that the conclusions are explicit, and clearly communicated. The paper thereby builds upon approaches for evidence integration that have already been published (Adami et al., 2011; Lavelle et al., 2012; Hart et al., 2010).

2. Methods/Approach: Assessment and integration of different evidence streams

Detailed discussion of the quality assessment of the individual evidence streams and a more in-depth discussion of the proposed evidence integration can be found in the over-arching guidance of the SETE) working group of the UK's independent COT and COC (SETE, 2021). An overview of the approach developed is provided in Figure 1 and key considerations are discussed in the following sections.

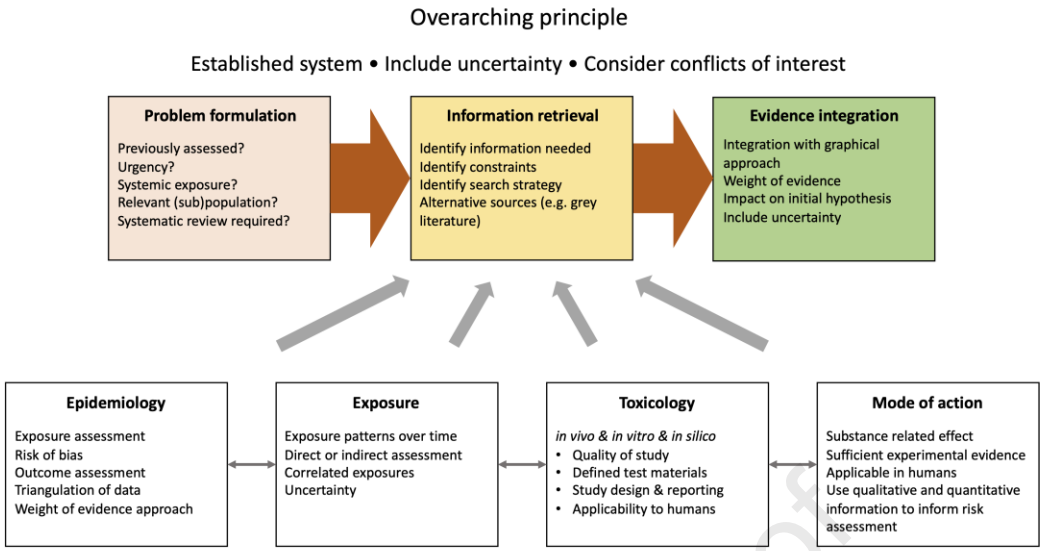


Figure 1: Overview of the key considerations for integrating different evidence streams, giving appropriate weight to each. Where possible, established systems should be used, and consideration should be given to uncertainties in the data. (Potential) conflicts of interest, especially where e.g. grey literature is used, should be clearly stated.

2.1 Problem Formulation and Information Retrieval

As a first (key) step, it is important to consider why a review or assessment is required, whether new information has become available, if a new potential risk has been identified, which population groups are to be addressed, and considerations whether individuals/groups could be at higher risk. This ensures that the right questions are asked, how urgently advice is needed, and helps make the most efficient use of resources and identifies the most appropriate approaches in a given situation. As information is retrieved and evaluated, the problem formulation may require refinement and additional aspects and considerations may be added. This should always be done in agreement with all relevant stakeholders.

It is important that the scope of the assessment is achievable and considers the available resources. A systematic review is the optimal process to ensure all available evidence has been identified and assessed, this is especially important the greater the consequence of an issue or if the risk requires quantification. However, an extensive systematic review is not necessary or possible in many situations and e.g. recent systematic reviews available in the literature or by an authoritative body can be utilised. Independent of the form of literature search, all studies relevant to the endpoint in question, independently of the format, should be documented and any changes to the initial search criteria should be recorded. All studies that provide relevant data should be included at this point, bearing in mind that the process begins with a specific question. However, the relevance and quality of studies will need to be established by assessing, e.g. compliance with appropriate guidelines, the relevance of the exposure, the nature of the adverse health outcome, uncertainties and potential bias (SETE, 2021).

2.2 Considerations on different evidence streams

In assessing risks to human health from exposure to chemical substances, relevant evidence/data comes from both experimental animals and human research, as well as *in vitro* and *in silico* studies. Depending on the issue (e.g. risk from exposure to a relatively new product), studies in experimental animals may provide the most valuable, and perhaps even the only, information, whereas in other situations (e.g. long-term and significant exposure to an environmental contaminant), epidemiological studies may provide the most relevant information.

For both epidemiological and toxicological information, a weight of evidence (WoE) approach should be applied, the specific details of the approach and

frameworks/guidance however may differ, depending on the information available. A prescriptive, generic checklist or numerical scoring approach is not advised as such an approach is likely to be limiting and inflexible. Epidemiological studies can provide direct evidence of human health impacts of specific exposures and it is recommended that, as far as possible, all relevant studies should be considered (Lawlor et al., 2016). The combination of individual studies can provide strong evidence, even if individually they may have different uncertainties and biases. *In vivo*, *in vitro* or *in silico* toxicological studies have the ability to identify adverse health effects of chemicals and provide mechanistic and experimental evidence for causal associations, although human relevance is not always clear. The quality of each study, using established criteria, for reliability, relevance and adequacy should be assessed. Such studies can form the basis of estimating a concentration/dose likely to be without appreciable effect in humans, if appropriate information is not available from human studies. This approach is generally considered to be protective, but it may (and indeed should) be modified if reliable scientific evidence is available (Dourson et al., 1996).

A mode of action (MOA) and its associated key events provide a powerful bridge between experimental studies (in animals, *in vitro* or *in silico*) and observations in human populations. It underpins the weight of evidence considerations by providing a mechanistic link between epidemiological observation and biological plausibility (Boobis et al, 2006; 2008; Meek et al, 2014). Thus, an adverse effect in experimental animals by a MOA that is considered relevant to humans would add appreciable weight to the assessment of causality underlying an association with this outcome observed in epidemiological studies, while a conclusion that a MOA is not relevant to

humans would argue against causality for the specific outcome in exposed subjects (Boobis et al, 2006; 2008; Meek et al, 2014).

Increasingly, new approach methodologies (NAMs), comprising a range of *in vitro* and *in silico* methods, are being used to assess the toxicological effects of chemicals. However, the use of NAMs for regulatory decision making is still at an early stage and hence current application is largely case-by-case. Guidance outlining best practice for the development and implementation of NAMs for regulatory use in human safety assessments are available (OECD, 2018; EURL ECVAM). However, while methods which have undergone formal validation are robust, transferable and widely trusted, the process of validation is time consuming and cannot keep pace with the advances driving the development of NAMs. For NAMs to be widely accepted in a future regulatory setting they need to be fit for purpose, with an emphasis on methodological reliability/performance, biological/toxicological relevance (e.g. linkage to key events) and interpretability for adverse effects *in vivo*.

Integrating data from NAMs with information from other sources, such as by developing adverse outcome pathways (AOPs) or MOAs, can provide an additional evidence stream in assessing qualitative and quantitative relationships between adverse health effects and exposure in human populations. When considering conclusions from new and yet to be validated, non-standard studies it is important to assess the adequacy and relevance of the method as well as the results, especially if a test system is far removed from humans (Kaltenhäuser et al., 2017).

Physiologically based pharmacokinetic (PBPK) modelling is particularly valuable for the quantitative integration of data generated using *in vitro* and *in silico* methods and may provide a means of bridging the exposure gap (Yoon et al., 2012). Studies with

unrealistic or unlikely exposure conditions for the general population may still provide valuable insights into findings observed (or lack of) in epidemiological studies under more relevant conditions. In assessing exposure, the emphasis is on assessing the totality of the available information, which includes different sources and routes of exposure, the assumptions and extrapolations made and the uncertainties that remain in the resulting estimates. During evidence integration, the rationales, and reasons for the choice of exposure information used for a given substance are provided and the consequences and uncertainties of these choices for the overall assessment are identified.

2.3 Evidence Integration

It is necessary to consider the overall picture when integrating evidence. No pre-existing hierarchy for the different lines of evidence should be applied; however, it is important to assess the confidence in the different lines of evidence and include this in considerations of causality. Rarely is the process unequivocal, where all evidence either supports or discounts a causal relationship. More often, information from epidemiological and toxicological data is ambiguous and hence initially assessing the strength of the lines of evidence separately will provide an indication of how reliable that line of evidence is and in turn allows for an informed decision on how a specific data set will influence the overall conclusion.

Building on previously published work as discussed above in Section 1, a number of key points need to be considered when integrating epidemiological and toxicological lines of evidence. These include whether a) the data indicate robust evidence of an effect in animals and b) the same effect has been reported in epidemiological studies. If the same effect has been reported in both animal and human studies,

consideration should be given as to how the effect levels compare. If possible, internal concentrations should be compared, together with the relative sensitivities of the molecular target and whether the effect concentration in the experimental studies reflects a realistic exposure scenario in the general population. Furthermore, consideration should be given to strain specific sensitivities to classes of compounds. Information on AOPs or MOAs can further strengthen (or weaken) the association between animal and human data and support for a biologically plausible causal relationship. Considerations should be thereby given to whether there is sufficient information to establish an MOE and whether the key events observed experimentally occur in exposed humans. *In vitro* data can provide further support for key events, if occurring at plausible concentrations, and are important to include in the integration considerations, together with any other mechanistic data.

If a predominantly positive answer can be given to the main considerations, then the WoE strongly supports causality. For example, *in vitro* data demonstrating that a key event occurs at the same tissue concentrations as estimated in the exposed population would add weight to a conclusion of causality, whereas the absence of effects in occupationally or accidentally exposed populations at or above levels at which effects are observed in experimental animals would reduce the weight of such a conclusion. Consideration should also be given to whether a line of evidence is considered sufficient by itself or provides a significant contribution to the overall WoE.

Considerations of the lines of evidence, their strengths and weaknesses, and specifically their influence on the conclusion should be clearly and transparently stated. To assist discussion about the influence of different evidence streams on the

conclusion and causality, but also to allow for clear and easy communication a visual representation of the conclusion of causality is recommended.

2.4 Constructing a Visual Representation for Causality

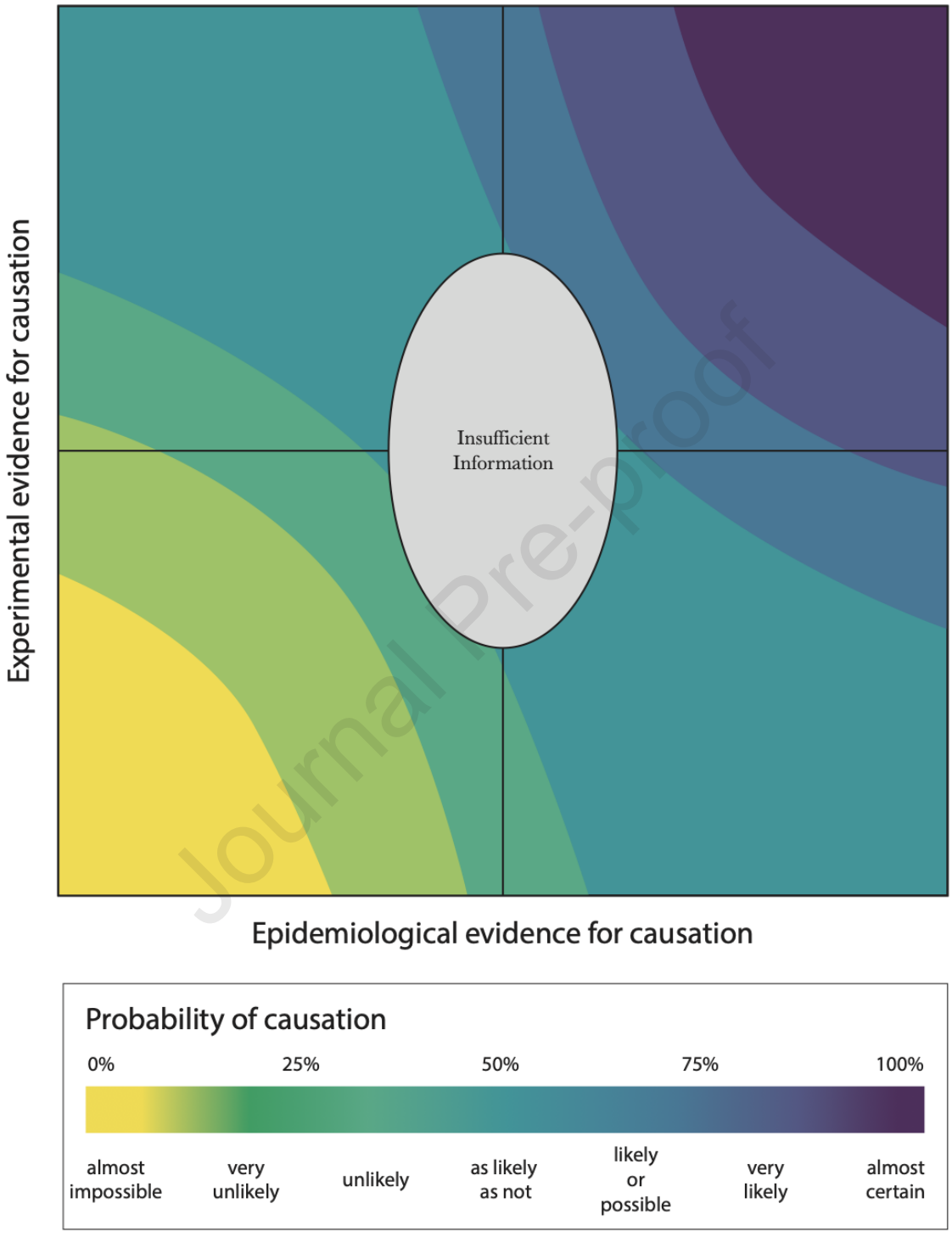
The visual representation, while a clear and easy way to communicate a conclusion on causality, should always be accompanied by in depth discussion of the WOE and underlying considerations by scientific experts.

Placement of the conclusion for a line of evidence on the probability of a causal relationship on the graph is qualitative and is a deliberative process, based on the considered professional judgment of the SAC. It requires assessment of all available data and reflects what should already be current practice in chemical risk assessment.

To support the construction of a visual representation it can be useful to establish a line of evidence table summarising the strengths and weaknesses of the data as well as the influence of the lines of evidence on the conclusion. This transparently outlines the extent to which the data contribute to a conclusion on causality.

When producing the visual representation, it is important to start with a clear hypothesis relating exposures to the substance of concern to adverse health effects in humans. This forms the initial estimate of causal inference and should be placed centrally in the grid. Depending on whether the toxicological, mechanistic or epidemiological evidence previously assessed supports or discounts (or has no clear influence on) a conclusion of causality, placement on the graph is moved accordingly, either in a positive or negative direction. The movement itself is influenced by the confidence in the initial estimate, using expert judgment, including

the impact of the strengths or weakness of the evidence, any relative weighing given to epidemiological and toxicological studies and the uncertainties associated with the data. Where possible estimates of uncertainty should be included, e.g. likely, upper and lower bound of impact. The final positioning on the graph should reflect the Committee's agreed conclusions on the weight of evidence on the likelihood of causation, i.e whether a causal relationship is likely/unlikely, possible but lacks strong experimental or epidemiological support or the information is insufficient to reach a conclusion. An example of such a visual representation is provided in Figure 2.



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217 Figure 2: Example for the visual representation of the likelihood of a causal

218 relationship, considering both epidemiological and experimental data. Causality and

219 placement on the graph are qualitative and based on professional judgment of the
220 whole database.

221 The colour scheme and presentation of probability follows the UK PHIA framework,
222 or probability yardstick. In contrast to other approaches, the axes should not be
223 considered numerical, and it is not intended that there is a quantitative relationship
224 between increments along an axis. Instead, positioning on the graph is the result of a
225 deliberative process and reflects the increasing or decreasing WoE based on expert
226 judgment on the likelihood (or not) of causation from exposure to a chemical leading
227 to an adverse outcome in exposed populations. Rather than a probabilistic or
228 numerical approach, the above visualisation is intended as a transparent means of
229 communicating the agreed conclusions. The final conclusion of the assessment
230 should be stated, with an estimate of the overall uncertainty and, where appropriate,
231 guidance on how data gaps could be filled.

232 While assessments of different evidence streams are often lengthy undertakings, as
233 more information is included in the process and/or becomes available, the placement
234 of the experimental and/or epidemiological evidence on the graph can be easily
235 adjusted.

236 **2.4.1 Example of evidence integration**

237 Cadmium, a contaminant with a well-established adverse effect, nephrotoxicity, was
238 chosen to illustrate the principles and considerations of the SETE guidance on
239 evidence integration. No full assessment of cadmium was undertaken but rather the
240 lines of evidence were drawn from previously published assessments (EFSA, 2009;
241 2011) and analysed for how these impacted on the WoE for a causal relationship
242 between cadmium exposure and nephrotoxicity. It should be stressed that the

243 following assessment is for illustrative purposes only; a full assessment would
244 require a much more deliberative process, including a comprehensive problem
245 formulation and WoE assessment.

246 Cadmium, in brief, primarily affects the kidney, especially the proximal tubular cells,
247 where it accumulates and may cause renal dysfunction. Cadmium can also cause
248 bone demineralisation (directly through bone damage or indirectly through renal
249 dysfunction). After prolonged and/or high exposure tubular damage may progress to
250 decreased glomerular filtration rate and eventually renal failure. It should be noted
251 that both EFSA (2009; 2011) and JECFA (FAO/WHO, 2011) identified renal toxicity
252 as the critical effect for establishing a health-based guidance value for cadmium. The
253 example presented here focused on nephrotoxicity.

254 The target organ (kidney) and the toxicokinetics after oral exposure are similar
255 among species, however the estimated absorption of cadmium in rodents is lower
256 compared to humans, especially after prolonged exposure. In addition, some species
257 differences in metallothionein synthesis, to which cadmium binds, cadmium kinetics
258 and toxicity have been well established.

Lines of evidence and their main strengths (S) and weaknesses (W)	**Influence on Conclusion**
Animal data S – The target organ (kidney) and the toxicokinetics after oral exposure are similar among species (including humans)	While there are species specific differences in metallothionein expression, cadmium kinetics and toxicity, these differences are well established and the animal data (target organs/endpoints) are in support of human findings

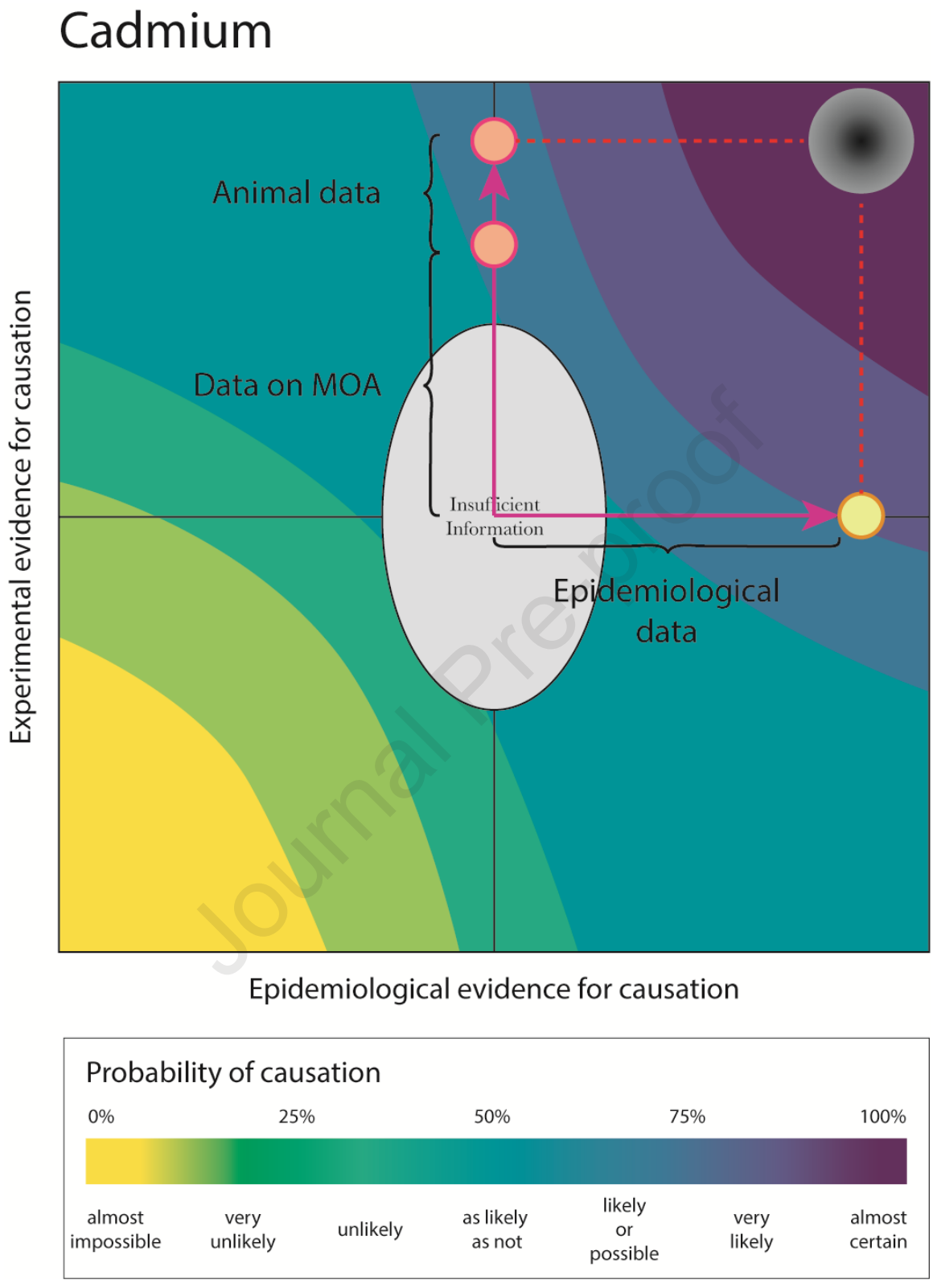
S – Cadmium is a clear nephrotoxin in experimental studies W – Estimated absorption of cadmium in rodents is lower compared to humans, especially after prolonged exposure	
Human data S – Consistent evidence that cadmium targets kidney after chronic exposure S – While renal toxicity is not as evident at low exposures, there is a clear indication of a positive dose-response relationship W –Results of cross-sectional studies affected by some degree of imprecision, which could cause an underestimation of true cadmium toxicity W – No firm conclusion on reversibility of renal damage, some data indicate possibility, others note glomerular dysfunction to progress even after contaminated soil replacement	Strong evidence that cadmium is a nephrotoxin from epidemiological studies and environmental exposure
Mechanistic data S – Link between the MOA, key events and human data	

Conclusions on causality	Epidemiological and experimental animal data and information on MOE provide strong evidence for a causal relationship between exposure to cadmium and renal toxicity.

Table 1: Summary of the strengths and weaknesses of the data on cadmium and the influence of the lines of evidence on the overall conclusion. Please note the lines of evidence and conclusions on the strengths and weaknesses have been drawn from previous evaluations and have not been systematically assessed here.

The available epidemiological studies provide consistent evidence that cadmium causes renal damage in some human populations. While the effect at low exposures is not as apparent, a positive dose-response relationship can be clearly identified, with increasing effect at increasing doses. Renal toxicity has been reported in epidemiological studies considering not only occupational exposures but also after environmental exposure or exposure through drinking water. The renal effect in humans is further supported by animal data, identifying cadmium as a classic nephrotoxin. While there are some species differences, specifically in metallothionein, cadmium kinetics and toxicity, these differences are well established and the animal data, i.e. target organs/endpoints, are in support of human findings. Both, epidemiological and experimental animal data provide strong evidence for a causal relationship between cadmium exposure and nephrotoxicity in humans. This is further supported by mechanistic data, providing a link between the MOA and human data.

For the recommended visualisation, the conclusion of a strong association of cadmium exposure and nephrotoxicity was applied. Starting in the middle of the graph and given the strong epidemiological evidence for such an association the marker was set to the far right. Both animal data and mechanistic data, here the MOA, also provide strong evidence for a causal association, hence the second marker was set near the top of the axis (again starting from the middle). The final conclusion on causality is visualised where the two lines intersect, and the final marker is placed. In this example, a causal association between cadmium exposure and nephrotoxicity, based on the consideration and integration of all available evidence, is almost certain.



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289 Figure 3: Visualisation of the likelihood for a causal relationship between cadmium
290 exposure and nephrotoxicity. The yellow circle is representative of all
291 epidemiological evidence assessed; the upper orange circle of all toxicological

evidence assessed. The lower orange circle indicates the impact of evidence on MOA on the conclusions. As all lines of evidence strongly suggest an effect, they have been moved to a place at the top (experimental) and far right (epidemiological). The grey circle represents the conclusion on causality from integration of all of the evidence and has been set where the individual lines of evidence intersect. Causality and placement on the graph are qualitative and based on professional judgment of the whole database.

3. Discussion and Conclusions

The aims of this paper are to build upon published approaches for evidence integration (Adami et al., 2011; Lavelle et al., 2012; Hart et al., 2010) and provide pragmatic guidance and transparent reflection on how the UK SACs review data and how different evidence streams should be integrated in a transparent manner, using graphical visualisation, giving appropriate weight to all.

Some work on how to integrate different evidence streams has been conducted at an international level. While existing approaches have certain aspects or steps in common, in general, they do not provide applicable and transparent guidance on how the actual evidence integration is/or should be undertaken. While the work here includes considerations on the same steps as in other approaches, i.e. problem formulation, literature retrieval and the assessment of the different evidence streams, by using established systems, the main focus is on the integration of different data sets and their visual representation. When integrating evidence, all lines of evidence should be considered, with no pre-existing hierarchy.

Good risk assessment practice involves a transparent description of consideration of the relevance of the endpoint(s) and adverse effects in/to human exposure, i.e. do

316 the data indicate a causal relationship, based on robust evidence of an effect in
317 animals and has the same effect been reported in epidemiological studies, as well as
318 whether the effect concentration in animals is of biological relevance in the general
319 population. Consideration should also be given to whether mechanistic data such as
320 information on AOPs or MOAs, are available as they can further strengthen (or
321 weaken) the support for a biologically plausible relationship. Information should also
322 be provided on potential biases/uncertainties in the data.

323 While this paper only briefly summarises the key aspects to be considered, reflecting
324 what should be current practice, further details are provided in the COT's and COC's
325 2021 SETE report (specifically Annex 1).

326 The novel aspect of this paper is the inclusion of a visual representation of the
327 conclusion on causality. This requires an explicit conclusion on the qualitative
328 contribution of the different lines of evidence on the probability of a causal
329 relationship between (usually) a specific adverse effect and exposure of the
330 population. The requirement to place a representation of this on the graph, means
331 that experts will need to agree a conclusion on the totality of the available data on a
332 line of evidence. The need to plot the different lines of evidence on the same graph
333 requires appropriate weighing of their relative contribution to the probability of
334 causation. Hence, visual representation provides a means for improving the
335 transparency and clarity of discussions on causation.

336 In addition, visual representation not only facilitates simple and clear communication
337 of the SAC's conclusion on causality, but also the influence that the different
338 evidence streams have on the final conclusion. This can help identify evidence gaps
339 and research needs. While the scale used for visualisation of probability follows a UK

government established system for communication of probability, in the scheme proposed here, conclusions on causality are qualitative, based on expert judgment, not quantitative. The further along the axes the circle is set, the more weight the data has been given in supporting a causal relationship. Where the different evidence streams intersect, the conclusion on causality is easily depicted and is a simple means of clearly indicating a consensus view. Again, the authors would like to stress that the movement on the graph is based on expert judgement and that the visualisation should always be accompanied by a detailed assessment of the underlying data.

Integration of information derived from epidemiological and toxicological studies requires an appreciation of the scientific processes around different disciplines to allow for an appropriate and balanced, evidence-based conclusion regarding causality. Ongoing communication among experts in the different disciplines is therefore essential to ensure a shared understanding of the question(s) to be addressed and the planned outputs of the risk assessment or other advice/evidence.

This overview provides an approach and a practical example of how such integration can be applied successfully.

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Highlights

- Approach to improve the consistency, transparency and communication of current practice of scientific advisory committees
- Emphasis is on weight of evidence and integration of different evidence streams, where all evidence is considered
- Visualisation tool is proposed, to help communicate the overall conclusion and contribution of different lines of evidence
- The conclusion on causality and its graphical representation is qualitative, and based on expert judgement
- Collaboration and ongoing dialogue between the different disciplines in risk assessment are strongly advised