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4 **Identifying the PECO: A framework for formulating good questions to explore the**  
5 **association of environmental and other exposures with health outcomes**  
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66  
67 **Conflict of interest**  
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69  
70 The authors declare they have no competing financial interests with respect to this manuscript, or  
71  
72 its content, or subject matter.  
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75 The views expressed are those of the authors and do not necessarily represent the views or  
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77 policies of the U.S. Environmental Protection Agency.  
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## PECO formulation guidance

A clearly-framed question creates the structure and delineates the approach to defining research objectives, conducting systematic reviews and developing health guidance [1, 2]. To assess the association between exposures and outcomes, including in the field of nutrition, environmental and occupational health, the concept of defining the Population (including animal species), Exposure, Comparator, and Outcomes (PECO) as pillars of the question is increasingly accepted [3, 4]. Thus, the PECO defines the objectives of the review or guideline. Furthermore, the PECO informs the study design or inclusion and exclusion criteria for a review, as well as facilitating the interpretation of the directness of the findings based on how well the actual research findings represent the original question.

Previously, we have recognized the importance of PECO for directing the assessments of benefits and harms, identification of exposures as risk factors or within risk assessments, and evaluation of the impact of interventions that prevent or mitigate an exposure or risk [3]; however, in debating PECO questions in our work, we found no guiding framework for operationalizing the PECO approach and the types of PECO questions researchers and decision-makers can answer. We identified only limited indirect guidance based on the development of Population, Intervention, Comparator, and Outcomes (PICO) questions where the general concept originated [1]. The Cochrane Collaboration emphasizes the importance of a well-formulated research question to guide an intervention review and provides clarity about the individual PICO components [5]; however, a review of 313 research studies reported that over half (54%) of the studies did not report on the four PICO components [6].

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171 In environmental, public and occupational health research, specific challenges exist with  
172 identifying the exposure and comparator within the PECO. In fact, in these fields there are  
173 fundamental differences to formulating questions about interventions and comparators in the  
174 PICO framework [1]. The Cochrane Handbook, widely recognized as reference guide for  
175 systematic reviews, does not specifically address the development of questions for *reviews of*  
176 *exposures* [5]. Other organizations have reported adapting PICO to PECO for studies of  
177 unintentional exposure [7-9]. For example, the Collaboration for Environmental Evidence  
178 recognizes the transition from PICO to PECO for questions about the effect of an exposure [7].  
179 The Navigation Guide, the National Toxicology Program's Office of Health Assessment and  
180 Translation, the U.S. Environmental Protection Agency's (EPA) Integrated Risk Information  
181 System (IRIS) and the European Food and Safety Association (EFSA) emphasize the role of the  
182 PECO question to guide the systematic review process for questions about exposures [8-10].  
183 EFSA also proposes a back-calculation of PECO elements to define an exposure (if the effect on  
184 the outcome is known among a determined population) [10]. Typically review authors have used  
185 approaches to PECO questions that are reflective of two of the scenarios that we will present,  
186 specifically cases where the research question aims to evaluate whether an exposure is associated  
187 with a health outcome(s). However, the PECO can also be focused in ways that can make the  
188 systematic review perhaps better suited to inform decision-makers and these are illustrated in  
189 three scenarios we will present. These latter PECO approaches are seldom used; in part this may  
190 be due to the fact that a fully developed framework for operationalizing the development of  
191 PECO questions does not exist.

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217 Given the lack of such guidance, research studies and systematic reviews often fail to explicitly  
218 state the PECO question. On the other hand, when reviews do start with a well-developed PECO  
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227 question, the purpose of the research is more clearly defined for the reader. For example, a recent  
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229 systematic review broadly explored whether or not exposure to serum or plasma  
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231 perfluorooctanoic acid (PFOA) among humans before or during pregnancy is associated with  
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233 fetal growth [11]. The authors reported that a 1 ng/mL increase in serum or plasma  
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235 perfluorooctanoic acid (PFOA) is associated with an 18.9 g decrease in birth weight. The review  
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237 appropriately specified the population, exposure, comparator and outcome and it focused on  
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239 exploring the presence or absence of an association. This approach is often chosen when little is  
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241 known about the exposure and its potential relationship to an outcome. An alternative way to  
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243 characterize with the impact of PFOA on health outcomes could better inform decision-makers.  
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245 For instance, one might ask which exposure level would lead to a dangerous decline in birth  
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247 weight or negative health outcomes in this population. If pursuing this strategy, evidence would  
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249 be needed to define the outcome of interest; in this example, although challenging, the protocol  
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251 would need to qualify the level of decline in birth weight that is considered harmful. Neither of  
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253 the two former approaches is superior or inferior; they simply describe different research  
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255 questions or phases in exploring the impact of exposures on outcomes. In fact, the general  
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257 approach to phrasing PECO questions will depend on a number of factors, including a) the  
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259 context; and b) what might be known about the effects of an exposure on an outcome at a given  
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261 time. However, because of the dependence on the research and decision-making context,  
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263 clarifying these aspects for the purpose of developing a PECO is crucial.  
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268 To address these issues, we developed a framework to formulate PECO questions that includes  
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270 five paradigmatic scenarios. These scenarios are common for researchers conducting individual  
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272 studies and authors of systematic reviews. Our framework proposes solutions with examples  
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274 (related to the topic of hearing impairment) to facilitate the creation of PECO questions with a  
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283 strong focus on the ‘E’ and ‘C’ domains (Table 1). This is because we consider defining the  
284 population (including animal populations) and outcomes as more straightforward given their  
285 relation to the existing PICO literature. We attempted to support our framework by examples.  
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290 Furthermore, for practical reasons our primary focus is on environmental health and we drew on  
291 selected examples from these fields; however, these scenarios are relevant to other disciplines,  
292 including broader public health questions and nutrition. Since the exploration of the existence of  
293 an association between an exposure and a comparator is the building block for any further  
294 evaluation, we will describe that scenario first. We follow with scenarios in which this evaluation  
295 has been done or, for some scenarios, the decision-making context may be known. As stated  
296 above, none of the approaches is superior to another and they are influenced by the context of  
297 what is known as we will lay out in this brief article.  
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308 Insert Table 1.  
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## 310 311 [Quantifying the exposure](#)

312 Research to understand and quantify the exposure is needed to properly address scenarios 2 to 5  
313 and formulate the PECO questions for them. In our first scenario, we describe what typically  
314 precedes those scenarios when little or nothing is known about the relationship between an  
315 exposure and outcome. Research addressing this scenario can provide information on the mean  
316 levels of exposure, ranges of exposures, and the nature of the association with the health  
317 outcome. In fact, for many organizations these are the most common questions asked. We will  
318 then present the remaining four scenarios with the assumption that research informing scenario 1  
319 is available.  
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339 To implement the framework, researchers can utilize a number of sources to inform and facilitate  
340 the quantification of an exposure and, specifically, to define the criteria for the comparator. We  
341 refer to this in many examples as a cut-off value. We use the term cut-off to broadly to refer to  
342 thresholds, levels, durations, means, medians, or ranges of exposure. In this commentary, our  
343 examples are informed by previously published primary research or systematic reviews and  
344 government identified thresholds (e.g. Occupational Safety Health Administration [OSHA]);  
345 however, other sources may include current legislation or a level which is considered to produce  
346 a minimally-important change.  
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## 356 357 **PECO Scenario 1** 358

359 The first scenario facilitates the identification of a comparison when little or nothing is known  
360 about the association between exposure and the outcome, including the nature of the relationship.  
361 This PECO, as stated one of the most common situations in environmental health, aims to  
362 explore the impact of different levels of exposure on health outcomes and the nature of the  
363 relationship. The comparator includes the entire range of exposures (e.g. an incremental increase  
364 in exposure). Here, all comparators are predefined by what the observed data will show. The  
365 objective may be to define whether or not there is an association between the exposure and  
366 health outcome and, if there is an association, to identify the nature of the relationship, e.g.,  
367 linear, logarithmic or u-shaped. For example, we present a summary of the results from two  
368 systematic reviews wherein this explorative PECO scenario leads to differing findings. In the  
369 first, a systematic review examined the association between 10 ng/mL increments of exposure to  
370 vitamin D and a range of health outcomes, including prostate cancer. The review reported no  
371 association between the 1,25(OH)<sub>2</sub>D biomarker to measure vitamin D with development of  
372 prostate cancer [12]. The second review examined the association between short-term exposure  
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395 to particulate mass with aerodynamic diameter less than 2.5 $\mu$ m (PM<sub>2.5</sub>) and suggested a positive  
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397 linear relationship with mortality from stroke [13].  
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400 In conjunction with Table 1, we provide additional examples to illustrate these scenarios using  
401 the topic of hearing impairment. To explore postnatal hearing impairment as a result of prenatal  
402 noise exposure, one may choose to examine an incremental increase in decibel (dB) exposure.  
403 Research suggests a linear dose-response relationship between the level of noise (i.e. dBs),  
404 duration of exposure, and health outcome of hearing impairment [14]; however, little is known  
405 about the effect of prenatal noise exposure on newborn hearing impairment [15]. Since there is  
406 insufficient information to isolate a specific comparison when examining prenatal noise  
407 exposure, we would develop a PECO that explores the association between incremental increase  
408 in exposure and hearing impairment. The size of the increments of the comparator may be  
409 informed by existing rationale or, if no evidence exists, they may require a more arbitrary  
410 identification. When developing a scenario about prenatal noise exposure, we present a  
411 hypothetical PECO question to reflect this situation, understanding that the ‘E’ and the ‘C’ could  
412 represent different values or smaller increments to measure change in the outcomes. For this  
413 example, we derived the incremental increase from the OSHA’s Standardized Threshold Shift  
414 for occupational noise exposure of 10 dB [16].  
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433 P: Among newborns, what is the effect of  
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436 E: 10 dB exposure to noise during gestation versus  
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439 C: 10 dB incremental increase on  
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442 O: Postnatal hearing impairment  
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## PECO Scenario 2

In the second scenario, we are interested in comparing health effects of different exposure levels but either do not know naturally occurring exposure levels or are unsure about which cut-offs to choose. This scenario is often a direct consequence of scenario 1 and may be addressed in the same systematic review as scenario 1 from which it would follow. Scientists often present data in ordinal groups (e.g. quartiles) in such situations. For example, we previously reported the effects of different levels of antioxidant blood and serum levels on pulmonary function and respiratory health [17-19]. The choice for the exposure and comparator in a systematic review may therefore be based on measures of distribution of the exposure in the included studies (e.g., central tendency values; highest versus lowest exposure groups such tertiles, quartiles, or quintiles). Ideally, the included studies describe the rationale for presentation of the exposure distribution to facilitate defining the cut-offs for the systematic review. This scenario requires exploration of the data to determine the specific exposure and comparator. It requires iterative development of the PECO based on findings from the systematic review or information from risk-management conclusions, which, nevertheless, should be pre-specified in a protocol. An additional example examines the effect of prenatal exposure to noise on postnatal hearing impairment.

P: Among newborns, what is the effect of

E: Highest noise exposure during pregnancy versus

C: Lowest noise exposure during pregnancy on

O: Postnatal hearing impairment

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507 In addition, this second scenario could be informed by baseline risk data from a population-level  
508 study that allows specifying the exposure of the comparison. For example, by using the  
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512 disaggregated population-weighted mean concentrations of PM<sub>2.5</sub> [20].  
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### 515 PECO Scenario 3 516

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518 Our third scenario addresses formulating a PECO question in which we might have information  
519 about a certain exposure level for a population of interest but want to compare that to the impact  
520 of a different level of exposure on a certain health outcome. In this situation the mean cut-offs  
521 from an external or general population (from other research) may serve as the comparator. For  
522 example, we may be interested in comparing the impact of exposure to PM<sub>2.5</sub> from one country  
523 to either a different country or a global mean. To do this we could use the data reporting PM<sub>2.5</sub>  
524 levels on the outcome of airflow obstruction from a nationally-representative survey in China as  
525 our exposure and outcome of interest. The comparator could then be informed by either the mean  
526 concentration of PM<sub>2.5</sub> levels in a different country or the global population-weighted mean  
527 concentration of PM<sub>2.5</sub> levels [20]. The systematic review would address the following PECO:  
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539 “In people exposed to particulate matter, what is the impact of levels of exposure identified in  
540 China compared to other countries or the global mean on airflow obstruction?” Of course, the  
541 ensuing analyses would have to carefully account for potential covariates or confounders.  
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546 A second example focuses on the impact of noise exposure among commercial pilots on hearing  
547 impairment exposure-level estimates from a cohort study conducted in Sweden [21]. To compare  
548 the risk of hearing impairment among commercial pilots with other occupations or the general  
549 population, we could conduct a systematic review of the effects on hearing impairment using a  
550 references of exposure levels from other occupations.  
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563 P: Among commercial pilots, what is the effect of  
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566 E: Noise corresponding to their occupational exposure versus  
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569 C: Noise exposure experienced by people in low-exposure occupations on  
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572 O: Hearing impairment.  
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#### 575 **PECO Scenario 4** 576

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578 In the fourth scenario, we may have sufficient information about the exposure and outcome to  
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580 quantify a dose-response relation. Specifying the exposure and comparator will include using  
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582 existing exposure cut-offs (e.g., thresholds, levels, durations, means, medians, or ranges of  
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584 exposure) associated with the health outcomes of interest. For example, we may want to explore  
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586 long-term exposure to occupational noise levels greater than 80 dB, which increase the risk of  
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588 hearing impairment compared to lower levels [22].  
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591 P: Among industrial workers, what is the effect of  
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594 E: Occupational noise exposure < 80 dB versus  
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597 C: Occupational noise exposure  $\geq$  80 dB on  
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600 O: Hearing impairment.  
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604 The difference between this and the next scenario lies in the exploration (i.e. comparison) of  
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606 what an intervention can achieve and outcomes that are associated with defined exposure levels.  
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608 In other words, the PECO elements may be driven by the difference between a context which is  
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610 concerned with setting a limit (such as a permissible occupational exposure level) versus a  
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619 context concerned with estimating the potential efficacy of an intervention to modify an  
620 exposure and the outcome which is the topic of our fifth and last scenario.  
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## 623 624 **PECO Scenario 5**

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627 The fifth scenario typically occurs when there is evidence suggesting an association between an  
628 exposure and the outcome, such as the research suggesting a dose-response relationship between  
629 the level of noise and health outcome of hearing impairment referenced previously [14] (based  
630 on a PECO following scenario 1, table 1). If a decision-maker is interested in a specific exposure  
631 cut-off or intervention to mitigate the exposure through known interventions, they will ask  
632 systematic reviewers to conduct a review using the PECO framework that appropriately  
633 describes the health effects of exposures that are achievable or realistic in relation to a  
634 comparator.  
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645 A policy maker may want to know, in the absence of evidence evaluating the impact of an  
646 intervention or in the context of new interventions for which high certainty evidence is available,  
647 what the potential impact of that intervention is on health effects. As direct evidence evaluating  
648 the intervention is not available, the exposure cut-offs in the PECO question would be informed  
649 by the implementation of an intervention (e.g. the potential introduction of a novel street surface  
650 that can reduce noise levels by 20 dB) compared to not implementing the intervention. Note that  
651 this will still only provide indirect evidence for the effects of the intervention but can be helpful  
652 for modelling the impact if intervention studies are not available. The discrete PECO formulation  
653 of this example would be as follows:  
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665 P: Among the general population, what is the effect of  
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668 E: Noise levels that are 20 dB lower than  
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675 C: Current noise levels on  
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678 O: Hearing impairment.  
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## 681 **Summary and conclusions** 682

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684 Formulating informative questions is a prerequisite for conducting an evidence synthesis in  
685 systematic reviews. The PECO approach to question formulation supports the conduct of a  
686 systematic review, including formulating search and eligibility criteria, presenting outcomes, and  
687 the wording in guidelines of final recommendations. We found little guidance about how to  
688 formulate questions that deal with unintentional exposures and, therefore, developed a  
689 framework based on existing examples and in-depth discussion that will help those designing  
690 research studies and authors of systematic reviews dealing with all populations and outcomes.  
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694 Our framework supports understanding the nuances and differences that exist between the review  
695 (research) question, the subsequent and sometimes iterative definition of inclusion and exclusion  
696 criteria from the PECO (they may or may not cover the PECO very narrowly or broadly) and the  
697 interpretation of the directness of the identified evidence. The framework can also provide  
698 guidance for those conducting individual studies dealing with exposures. We recognize that  
699 additional considerations would be required to develop a PECO framework aimed at animal  
700 studies or systematic reviews that include consideration of epidemiological and animal studies to  
701 discern whether a chemical has an effect on a health outcome. We encourage further testing and  
702 feedback on the use of this framework and include Figure 1, as a brief guide to facilitate the  
703 identification and development of an optimal PECO question.  
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## Acknowledgments

None.

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## **Funding**

This research was supported by the MacGRADE Centre at the McMaster University.

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842  
843 **Author contributions**  
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845 RLM and HJS conceptualized the approach and PW and KAT contributed to it. RLM and HJS  
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847 wrote the manuscript. PW and KAT critically revised the manuscript for important intellectual  
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849 content. All authors approved of the final version.  
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Table 1. Five paradigmatic approaches and examples for identifying the exposure and comparator in systematic review and decision-making questions

<b>Potential systematic-review or research context</b>	<b>Approach</b>	<b>PECO example</b>
1. Calculate the health effect from an exposure; describing the dose-effect relationship between an exposure and an outcome for risk characterisation.	Explore the shape and distribution of the relationship between the exposure and the outcome in the systematic review.	Among newborns, what is the incremental effect of 10 dB increase during gestation on postnatal hearing impairment?
2. Evaluate the effect of an exposure cut-off on health outcomes, when the cut-off can be informed iteratively by the results of the systematic review.	Use cut-offs defined based on distribution in the studies identified in the systematic review.	Among newborns, what is the effect of the highest dB exposure compared to the lowest dB exposure (e.g. identified tertiles, quartiles, or quintiles) during pregnancy on postnatal hearing impairment?
3. Evaluate the association between an exposure cut-off and a comparison cut-off, when the cut-offs can be identified or are known from other populations.	Use mean cut-offs from external or other populations (may come from other research).	Among commercial pilots, what is the effect of noise corresponding to occupational exposure compared to noise exposure experienced in other occupations on hearing impairment?
4. Identify an exposure cut-off that ameliorates the effects on health outcomes.	Use existing exposure cut-offs associated with known health outcomes of interest.	Among industrial workers, what is the effect of exposure to < 80 dB compared to ≥ 80 dB on hearing impairment?
5. Evaluate the potential effect of a cut-off* that can be achieved through an intervention to ameliorate the effects of exposure on health outcomes.	Select the comparator based on what exposure cut-offs can be achieved through an intervention.	Among the general population, what is the effect of an intervention that reduces noise levels by 20 dB compared to no intervention on hearing impairment?

\* Cut-offs is a broad term referring to thresholds, levels, durations, ranges, means, medians, or ranges of exposure. dB: decibel; PECO: population, exposure, comparator, outcome(s).