This leaflet provides an overview of Parkkinen et al. (2018).

1. The flow of evidence
Clinical studies (especially large, well-conducted randomised studies) can suffice to establish causation. But mechanistic studies can raise or lower the credibility of a causal claim by supporting or undermining the existence of a mechanism of action:

- **A is a cause of B**
- **A is correlated with B**
- **There is a mechanism of action**

Specific mechanism hypotheses

Clinical studies: measure A and B together

Mechanistic studies: evidence of mech. features

2. Efficacy and external validity

**Efficacy.** Does the causal relationship hold in the study population?

**External validity.** Can the causal relationship in the study population be extrapolated to a target population of interest?

3. Gathering evidence of mechanisms

4. Evaluating evidence of mechanisms

Each specific hypothesised mechanism of action is assessed by analysing the methods, implementation and results of mechanistic studies:

- **Specific mechanistic hypotheses; mechanistic studies**
- **Evaluate general mechanistic claim**
- **Present evaluation**

The status of the general mechanistic claim (GMC) depends on evidence from both mechanistic and clinical studies:

<table>
<thead>
<tr>
<th>Status of the GMC on the basis of mechanistic studies</th>
<th>Status of the GMC on the basis of clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established</td>
<td>Established</td>
</tr>
<tr>
<td>Provisionally established</td>
<td>Provisionally established</td>
</tr>
<tr>
<td>Arguable</td>
<td>Arguable</td>
</tr>
<tr>
<td>Speculative</td>
<td>Speculative</td>
</tr>
<tr>
<td>Arguably false</td>
<td>Arguably false</td>
</tr>
</tbody>
</table>

5. Using evidence of mechanisms

**Efficacy.** Status of causal claim = minimum of status of correlation claim and status of general mechanistic claim.

**External validity.** The status of the causal claim in the target population depends on the status of the causal claim in the source population, the status of the claim that the mechanism of action in source and target is similar, and the status of the causal claim in the target population on the basis only of studies carried out on the target population:

<table>
<thead>
<tr>
<th>Causation in source population + similarity of mechanism in target and source</th>
<th>Causation in target population + similarity of mechanism in source and target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established established, or Provisionally established, or Other combinations</td>
<td>Established, or Provisionally established, or Other combinations</td>
</tr>
<tr>
<td>Provisionally ruled out, established, or Provisionally established, or Other combinations</td>
<td>Provisionally ruled out, established, or Provisionally established, or Other combinations</td>
</tr>
</tbody>
</table>

Appendices

In several appendices, Parkkinen et al. (2018) provide further discussion of the above approach.

**A. A critical appraisal tool for evidence of mechanisms.** A checklist of questions to ask when evaluating evidence of mechanisms.

**B. GRADE-style tables with mechanism assessment.** Shows how GRADE tables for the assessment of clinical studies can be extended to incorporate the assessment of hypothesised mechanisms of action.

**C. Databases for evidence of mechanisms.** Some examples of databases that can assist the search for relevant mechanistic studies.

**D. Assessing exposures.** How the framework applies to the assessment of exposures to possible harms, and its relation to other approaches, such as SYRINA and that of IARC.

**E. Assessing mechanisms in public health.** Considerations to bear in mind when applying the framework to public health interventions.

**F. Particularisation to an individual.** How to apply the framework to the treatment of an individual.

**G. A probabilistic interpretation of quality and status.** Shows that the general approach is compatible with a more quantitative Bayesian framework.

**H. Glossary.** Definitions of key terms.

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Bibliography