

**AOP 173 - Substance interaction with the pulmonary resident cell membrane components leading to pulmonary fibrosis**  
**Submission for WNT/WPHA endorsement – 5 September - 13 October 2023**

Comments were received from Germany

Country	Page #	Comments	Response from AOP developers
Germany	19-21	<p>The concept of associative events has not been defined or discussed yet on OECD level. It seems that the associative events can be induced via other pathways and may modulate effects through AOP 173, but for which there is a lack of convincing evidence that they are essential to toxicity along AOP 173. Before defining a new category of events, it should be checked if these events would be better characterized as modulating factors in the context of the present AOP.</p> <p>If a new category is needed, the authors should provide a definition that then would need a broader discussion before the concept can be generally introduced. A large number of associative events might make AOPs more difficult to understand and it might also be difficult to define clear criteria to distinguish KEs and AEs and/or AEs and modulating factors.</p>	<p>We thank the reviewer for these thoughtful comments. 'Associative events' have been part of AOP173 from the beginning and were further developed and a schematic developed to depict the connections, through the layers of the review process, while addressing reviewers' comments.</p> <p>However, we agree that it is a term that hasn't been defined in the guidance document and we do appreciate reviewers' concerns of retaining such a term. Thus, we have removed the term altogether from the document. We have moved the text associated with these events along with the schematic from Essentiality of KEs tables to the Quantitative considerations section. The revised document been shared with the reviewers.</p>