Domain of Applicability

The AOPs are not life stage specific

Essentiality of the Key Events

The biological plausibility of KERs is strong due to the available mechanistic evidence present in studies from a wide variety of taxa. Nrf2 inhibition cause oxidative stress and a variety of cellular responses. Jeong et al. used a weight-of-evidence approach in analyzing TOXCAST data, and proposed the putative AOP pathway from MIE Increased Reactive Oxygen Species to KE Oxidative Stress to KE Increase, Inflammation.

The essentiality of KERs is strong due to a variety of evidence from different controlled experimental designs with controls. Exposure to a variety of chemical stressors have induced oxidative stress from Nrf2 inhibition. In this AOP we are focusing on the KERs between Nrf2 inhibition, oxidative stress, inflammation, vascular endothelial dysfunction, angiogenesis disfunction, vascular disrupting effects. Support for the essentiality of the key events can be obtained from a wide diversity of taxonomic groups, with lab rats, cell lines, and zebrafish.

The empirical support of KERs is largely found in toxicological studies derived from reference chemicals with dose-response and temporal concordance assessed.

Evidence Assessment

The QWOE approach is an analytical method that utilizes causality criteria to assess the evidence-supported postulated AOP[4]. Firstly, the hypothesis of action was presented and the quantitative evaluation of evidence ranging from no evidence (0) to strong for each category (3, strong and −3, strong counter) utilizing the evolved MIEs, KEs, and KERs. Subsequently, a ranked importance-based numerical weight was assigned to Bradford Hill causal considerations, and the composite score and confidence score for MIEs, KEs, and entire AOP were evaluated.

Assigned weigualitative rating						
		MIE	KE1	KE2	KE3	KE4
Biological plausibility	in vivo and in vitro evidence suggest that the PFAs can cause the hepatot					
Essentiality empirical support	0.4	1	1	1	1	1
Dose and incidence concordance	0.2	3	3	3	3	3
Empirical support temporal concordance	0.2	3	3	3	3	3
Consistency across test systems	0.1	3	3	3	3	3
Analogy mutiple studies support KE and KER	0.1	3	3	3	3	3
Score	1	2.2	2.2	2.2	2.2	2.2
AOP Score	0.733333					

Known Modulating Factors

Modulating factors (MFs) may alter the shape of the response-response function that describes the quantitative relationship between two KES, thus having an impact on the progression of the pathway or the severity of the AO. The evidence supporting the influence of various modulating factors is assembled within the individual KERs.

Quantitative Understanding

Optional field to provide quantitative weight of evidence descriptors.