Abstract: Asbestos fiber toxicity and the risk of malignant disease is dependent on fiber dose, type, and dimension. Although the precise mechanistic pathways by which asbestos fibers cause a tumorigenic response have not been elucidated, one of several proposed mechanisms is through asbestos-induced genotoxic and mutagenic effects. While the historical regulatory approach to dose-response modeling of DNA-reactive compounds has been the linear no-threshold cancer model, alternative threshold models have gained some acceptance when the appropriate evidence for a threshold mode-of-action (MOA) exists. To evaluate the available evidence for an indirect vs. direct MOA for asbestos, this analysis critically assessed over 130 genotoxicity in vivo and in vitro studies of asbestos fibers with respect to: 1) assays utilized to address an indirect vs. direct MOA, and 2) assay dose and fiber type used in relation to relevant human equivalent doses in occupationally-exposed individuals. Most in vivo studies were not informative to address the question of an indirect vs. direct MOA. Of the 46 in vitro studies that evaluated indirect vs. direct effects, the overwhelming evidence suggests that the genotoxic action of asbestos fibers occurs through indirect mechanisms, such as ROS generation. Additionally, the human equivalent doses utilized in the in vitro and in vivo genotoxicity assays were several orders of magnitude greater than the median and upper bound fiber lung burdens observed in heavily exposed workers (253,000 and 8,540,000 f/g, respectively), as well as over 11,000-fold greater than lung fiber burdens found in individuals with pleural plaques. This analysis provides a current weight-of-evidence for the genotoxic MOA of asbestos fibers and supports the role of cellular thresholds for indirect asbestos-induced genotoxic effects. This study provides critical information for risk assessors to form a basis for selection of dose-response models that attempt to understand carcinogenic risks to asbestos at low levels of exposure.