Nuclear power plant disasters have severe and far-reaching consequences requiring rapid and expert response to mitigate the disaster scope. Limiting modeling & simulation (M&S) assessment of alternative interventions is lack of integration and interoperability of legacy nuclear reactor models with human-oriented avatar or agent-based simulations. This research proposes a generalizable approach to bridge this gap. The approach proposed begins with conceptual model (CM) that broadens the scope of legacy stovepipe nuclear simulations using a System of System (SoS) perspective. Next, instantiating the SoS onto a live, virtual and constructive (LVC) simulation framework enables interoperability of nuclear models with LVC simulations such as simulations of emergent unmanned aerial system (UAS). The approach next reduces factor complexity inherent to LVC simulation through a factor screening experiment suitable for replication of potential nuclear disasters including the Fukushima-like Spent Fuel Pool crisis. As a prototypical implementation using the framework constructive component, this research demonstrates a system analysis of competing UAS platforms intervening to prevent a SFP disaster. The SoS CM, LVC simulation framework, factoring screening, and prototypical implementation are generalizable to other nuclear disaster scenarios. Further, the SoS approach advances analysis in system life cycle phases including concept exploration, system design, engineering, training, and mission rehearsal. Live, virtual, and constructive component subsystems of the CM are described along with an explanation of input/output requirements. Finally, applications to analysis and training, an evaluation of the SoS CM based on recently proposed criteria found in the literature, and suggestions for future research are discussed.