A wealth of available biological data such as those from EPA’s ToxCast Phase I (http://www.epa.gov/ncct/toxcast/) requires new computational approaches to link chemical structure, short-term bioassay results, and chronic in vivo toxicity responses. We advance the predictive QSAR modeling workflow that relies on effective statistical model validation routines and implements both chemical and biological (i.e., in vitro assay results) descriptors of molecules to develop in vivo chemical toxicity models. We have developed two distinct methodologies for in vivo toxicity prediction utilizing both chemical and biological descriptors. In the first approach, we employ biological descriptors directly in combination with chemical descriptors to build models. Obviously, this approach requires the knowledge of biological descriptors to make toxicity assessment for new compounds. Our second modeling approach employs the explicit relationship between in vitro and in vivo data as part of a two-step hierarchical modeling strategy. First, binary QSAR models using chemical descriptors only is built to partition compounds into classes defined by patterns of in vitro – in vivo relationships. Second, class specific conventional QSAR models are built, also using chemical descriptors only. Thus, this hierarchical strategy ultimately affords the external predictions using chemical descriptors only. We will present the results of applying both strategies to ToxCast Phase I and similar data. Our studies suggest that utilizing in vitro assay results as biological descriptors afford prediction accuracy that is superior to both the conventional QSAR modeling that utilizes chemical descriptors only or in vivo effect classifiers based on in vitro biological response only.