Extant process-based hydrologic and water quality models are indispensable to water resources planning and environmental management. However, models are only approximations of real systems and often calibrated with incomplete and uncertain data. Reliable estimates, or perhaps further reduction of prediction uncertainty, contribute directly to successful risk management and the formulation of environmental policy. This paper discusses widely used and promising methods for estimating model prediction uncertainty in complex environmental systems; and lays down a framework for probabilistic risk management and its application to one of the most important watershed-based regulatory programs, the Total Maximum Daily Loading (TMDL). In TMDL development, a margin of safety (MOS) is applied to account for the uncertainty embedded in the analysis or modeling exercise. However, in most TMDL developments, MOS is arbitrarily selected and the related degree of protection provided by the safety factor often remains unknown. A formal risk-based approach linking required load reduction in a TMDL to the analysis uncertainty and required degree of protection is presented along with a formal estimation of MOS. Bayesian-based probabilistic approaches, such as Classical Bayesian Estimation (BEA), Generalized Likelihood Uncertainty Estimation (GLUE), and Ensemble Kalman Filter (EnKF) hold promise for TMDL development under conditions of uncertainty. Current TMDL practices need to be revised taking into consideration recent advances in model uncertainty estimation. The paper ends with a list of future challenges in uncertainty estimation and research needs to reduce its magnitude.