Anthropogenic changes in the composition of the atmosphere and land uses certainly affect climate and hydrological responses in a cause-and-effect relationship. However, an accurate deterministic prediction of future hydro-climatic regimes, incorporating anthropogenic effects, may be infeasible. Obvious sources of uncertainty are the weaknesses of climatic and hydrological models. Besides, uncertainty may be also a structural and inevitable characteristic of the related processes, as the atmosphere and hydrological basins are inherently too complex systems. Quantification of uncertainty in probabilistic terms can be regarded as a more feasible alternative in comparison to the elimination of uncertainty. However, the quantification of (the increase of) uncertainty under future conditions, including anthropogenic effects, is hardly achievable at present. A small feasible step is the quantification of uncertainty under present and past conditions. This has been seriously underestimated and underrated so far. Climatic models describe a portion of natural variability and result in interannual variability that is commonly too weak. Hydrological models tend to smooth out variability of hydrological processes. Even probabilistic approaches based on classical statistical analyses of real world data hide some sources of variability and uncertainty, especially the ones related to the omnipresent long-term persistence of natural processes. The latter approaches, however, can be adapted towards making their estimations closer to reality, thus resulting in more accurate yet impressively higher estimates of uncertainty. These ideas and questions are illustrated by means of a case study dealing with hydrological modelling and water resources management in a Greek catchment.