Common waterhemp (Amaranthus rudis Sauer) is the most prominent and troublesome weed in agronomic crops in Missouri, Iowa, and Illinois. As of 2014 in the U.S., herbicide resistance was present in waterhemp to one or more of the following herbicide modes of action: growth regulators, EPSPS-, acetolactate synthase (ALS)-, protoporphyrinogen (PPO)-, photosystem II (PSII)-, and 4-hydroxyphenylpyruvate dioxygenase (HPPD)-inhibiting herbicides. The objectives of this research were 1) determine the effect of cultural and herbicidal control methods on resistant waterhemp in glufosinate-resistant soybean, 2) evaluate weed management programs and response of HPPD-resistant soybean to HPPD-inhibiting herbicides, and 3) investigate the distribution of herbicide resistances and molecular mechanisms conferring resistance in Missouri waterhemp populations. Results from this research indicate that preemergence followed by postemergence with residual (PRE fb POST w/RES) herbicide programs with 19- or 38-cm rows will provide the greatest glyphosate-resistant (GR) waterhemp control in glufosinate resistant soybean. PRE fb POST programs improved GR waterhemp control and biomass reduction over all one- and two-pass POST programs in HPPD-resistant soybean. The addition of isoxaflutole to PRE treatments in HPPD- resistant soybean was not always necessary to provide high levels of weed control, but incorporating isoxaflutole or mesotrione in PRE fb POST programs allows for a greater diversity of effective herbicide modes of action. Resistance to five major herbicide modes of action was confirmed with at least 52% of 187 waterhemp populations being resistant to two modes of action. Results indicate PRE fb POST programs with multiple, effective modes of action will be necessary to control Missouri waterhemp populations in the future.