The southern US produces 90% of the nation’s cotton with the Texas High Plains being the largest contiguous region. Since 2011, Texas cotton production has been severely challenged by the presence of glyphosate-resistant Palmer amaranth (Amaranthus palmeri S. Watson) indicating alternative systems without heavy reliance on glyphosate are needed. Integrating soil residual herbicides into a weed management program is an effective strategy to control glyphosate resistant weeds before they emerge. BASF Corporation is developing hydroxyphenylpyruvate dioxygenase (HPPD) tolerant cotton, which will allow growers to use isoxaflutole in future weed management programs. In 2019 and 2020, field experiments were conducted at New Deal, Lubbock, and Halfway, Texas to evaluate HPPD-tolerant cotton response to isoxaflutole applied preemergence (PRE) or early-postemergence (EPOST) as well as to determine the efficacy of isoxaflutole when used as part of a weed management program. Crop response experiments at New Deal and Lubbock included: Caparol at 38.4 fl oz/A PRE followed by (fb) Liberty at 43 fl oz/A + Dual Magnum at 21.33 fl oz/A EPOST, isoxaflutole at 3 fl oz/A + Caparol PRE fb Outlook at 16 fl oz/A + Liberty EPOST, isoxaflutole + Prowl at 32 fl oz/A PRE fb Outlook + Liberty EPOST, isoxaflutole + Caparol + Prowl PRE fb Outlook + Liberty EPOST, isoxaflutole + Caparol at 19.2 fl oz/A PRE fb Liberty + Dual Magnum EPOST, isoxaflutole + Caparol PRE fb Liberty + Dual Magnum EPOST, isoxaflutole + Cotoran at 32 fl oz/A PRE fb Liberty + Dual Magnum EPOST, Caparol PRE fb isoxaflutole + Liberty EPOST, and Caparol PRE fb isoxaflutole + Liberty + Roundup at 44 fl oz/A EPOST. A blanket mid-postemergence (MPOST) Roundup + Liberty application was made at first bloom and some treatments received diuron at 32 fl oz/A postemergence-directed (PDIR) when cotton was at the bloom stage. At New Deal, cotton response was greatest following the EPOST application, but did not exceed 10%. Cotton response to isoxaflutole was greatest following the PRE application at Lubbock in 2019, but never exceeded 14%. In 2020 at Lubbock, cotton was replanted due to severe weather. There was <1% cotton response following the PRE application and maximum cotton response observed was 9% following EPOST and MPOST applications of isoxaflutole + Caparol at 19.2 fl oz/A and isoxaflutole + Fluometuron, both fb Liberty + Dual Magnum. By late season, no cotton response was detectable. There was no difference in cotton stand at either location. Cotton lint yield ranged from 1,082-1,271 lb/A at New Deal and 602-676 and 1,377-1,542 lb/A in Lubbock in 2019 and 2020, respectively. Lint yields were not different from the nontreated weed-free control. In a non-crop weed control study at Halfway, treatments mimicked the cotton response trials with the addition of: isoxaflutole + Caparol PRE fb Roundup + Engenia at 12.8 fl oz/A EPOST and Caparol PRE fb isoxaflutole + Roundup + Engenia EPOST. These two treatments included Roundup + Engenia MPOST. All PRE treatments containing isoxaflutole controlled Palmer amaranth ≥94% 14 and 21 days after treatment. All treatments controlled Palmer amaranth ≥94% 21 days after the EPOST application. Twenty-one days after the MPOST treatment, systems with isoxaflutole EPOST controlled Palmer amaranth 88-93% while systems with isoxaflutole PRE controlled Palmer amaranth 94-98%. End of season Palmer amaranth control was lowest in the system without isoxaflutole (88%) and when isoxaflutole was used EPOST (88-91%). When used as part of an overall weed management program, the opportunity to use isoxaflutole in cotton will improve season-long control of Palmer amaranth with no adverse effects on cotton yield and quality.