The main mechanism of toxicity of the insecticide chlorpyrifos (CPF) is related to the ability of its oxon metabolite to bind and inhibit acetylcholinesterase (ChE) in the central and peripheral nervous systems. Concerns were raised about CPF regulatory standards based on its inhibitory effects on ChE activity that may overlook more sensitive non-cholinergic mechanisms. Increasing evidence points to CPF effects on the nervous system development in mammals and zebrafish (ZF) at exposures below those that inhibit ChE (ChEI). Noncholinergic mechanisms are suggested for CPF neurodevelopmental toxicity and this is important when deciding weight-of-evidence (WoE) in pesticide risk characterization. We reviewed in vivo data and the in vitro CPF Toxicity Forecaster (ToxCast) database to assess the WoE for noncholinergic effects at low CPF exposure. There were no true actives in ToxCast assay results (only cytotoxicity). In vivo studies with rat pups showed that CPF at 0.5 mg/kg/d disrupted CNS cannabinoid and dopamine metabolism, and induced behavioral effects in the absence of brain ChEI. Epidemiological data showed long-lasting deficits in working memory and effects on brain morphology in children aged 3-13 years after in utero CPF exposure. A PBPK-PD model is currently being used by regulatory agencies for estimating reference doses is based on 10% RBC AchEI from human studies. The estimated oral human Point of Departure (PoD) for steady state (21-day: most relevant scenario for in utero human) exposure was 780 ng/kg. Others used this PBPK-PD model with the same human data to estimate the CPF maternal exposure that would by necessary to produce decrements in their child’s working memory at 7 yr. From these estimates the oral in utero PoD for working memory decrements was 3.4-fold lower than the 780 ng/kg predicted by the PBPK-PD model for 10% RBC ChEI. Supporting mammalian/human data, many ZF studies showed irreversible neurobehavioral deficits at 10-fold lower exposures (0.01 uM) than those inhibiting ChE (0.10 uM). These results provide WoE that the pathways impacted by CPF in the developing brain may be independent of ChE.