

Imidacloprid and Fipronil *In Vivo* Toxicity Endpoints Compared to ToxCast Profiles  
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Imidacloprid (IM) and fipronil (FP) are a new generation of insecticides with more selective toxicity to insects vs. humans for control of pests/parasites on crops and pets. IM is a nicotinic acetylcholine receptor (nAChR) agonist at the neuronal and neuromuscular junctions. FP (CNS toxin) blocks  $\gamma$ -aminobutyric acid (GABA)-gated Cl<sup>-</sup> channels. To investigate potential use of USEPA's ToxCast high-throughput screening assays (HTS including zebrafish, ZF) in risk assessment we first reviewed available *in vivo* animal toxicity studies to establish toxic endpoints and no-observed-effect-levels. We then examined ToxCast data for indications of pathway disruptions that could lead to effects manifested as overt toxicity. *In vivo toxicities*: Both showed neurotoxicity, developmental neurotoxicity (DNT) and thyroid, liver and kidney pathology and were potent inducers of the hepatic CYP enzymes. In chronic rodent bioassays FP caused thyroid and liver neoplasia. USEPA considers IM an unlikely carcinogen (Group E), whereas FP is classified as a Group C (possible human) carcinogen based on thyroid follicular cell tumors in rat. *Positive ToxCast data*: IM: Brain nAChR ion-channels, liver cell PXR activation associated with liver CYP induction and ZF (mortality). FP: Numerous pathways for thyroid and liver cancer metastasis, chronic inflammation, oxidative stress, mitochondrial alterations, indicators of tissue-damage, regrowth and repair (angiogenesis, growth signaling, tissue remodeling). FP had positive associations between the rat thyroid lesions and assays for human genes (CXCL10 & TP53) linked to thyroid cancer hallmark processes. FP was positive in ZF assays for malformations (axis, yolk sac & pericardial edema) and DNT. ToxCast assays were predictive of targets and activities relative to *in vivo* IM and FP endpoints. Pesticides like IM and FP, with complete *in vivo* databases, can be used for validation of ToxCast predictive toxicity models. HTS profiles may also be used to support modes of action and adverse outcome pathways for human risk assessment.