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A comparison of fish pesticide metabolic pathways with those of the rat and goat

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ABSTRACT

Ecological risk assessments are often limited in their ability to consider metabolic transformations for fish species due to a lack of data. When these types of evaluations are attempted they are often based on parent chemical only, or by assuming similarity to available mammalian metabolic pathways. The metabolism maps for five pesticides (fluazinam, halauxifen-methyl, kresoxim-methyl, mandestrobin, and tolclofos-methyl) were compared across three species. A rapid and transparent process, utilizing a database of systematically collected information for rat, goat, and fish (bluegill or rainbow trout), and using data evaluation tools in the previously described metabolism pathway software system MetaPath, is presented. The approach demonstrates how comparisons of metabolic maps across species are aided by considering the sample matrix in which metabolites were quantified for each species, differences in analytical methods used to identify metabolites in each study, and the relative amounts of metabolites quantified. By incorporating these considerations, more extensive rat and goat metabolism maps were found to be useful predictors of the more limited metabolism of the five pesticides in fish.

1. Introduction

One aspect of species extrapolation for assessing ecological risk that can be relevant both to exposure and effects characterizations is understanding xenobiotic metabolism, both as a means of detoxification as well as bioactivation. Additionally, comparison of metabolism pathways across species serves to provide better understanding where similarities and differences exist in biotransformation reactions that may lead to enhanced toxicity. This can then serve as a basis for predicting metabolism for an untested species based on known metabolic maps for tested species. Where rules can be formulated for cross-species metabolism based on transformation pathways leading to enhanced toxicity or detoxification, predictions of altered susceptibility due to species differences in metabolism can be used to better evaluate risk where empirical metabolism data is lacking.

Due to data requirements under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for the registration of pesticides, information on metabolic pathways is relatively rich for certain individual pesticides, pesticide classes and certain animal species. For example, for pesticides used on food crops, metabolism data collected following internationally harmonized guidelines is submitted to the United States Environmental Protection Agency (USEPA) by registrants as part of the pesticide registration process. Understanding metabolism across species for pesticide chemicals where the data exists will allow for the extrapolation of concepts and lessons learned to data poor species and chemicals. For example, the same type of systematically collected data is not as available for industrial chemicals, and is limited for most species.

Data submissions for registration or re-registration of pesticides, particularly for chemicals used on food products typically includes the submission of rat metabolism and pharmacokinetic data (https://www.epa.gov/pesticide-registration/data-requirements-pesticide-registration). Depending on the use scenario, there may be information required on pesticide residues (parent chemical and metabolites) in plants and/or residues in livestock species. For environmental assessments, in addition to standard toxicity test data submitted on the parent chemical there is typically guideline study data in environmental organisms submitted on environmental degradation processes. Environmental degradates may arise from a series of biotic or abiotic transformations for which there are more than a dozen guidelines specified. The required data submissions again depend on the proposed use of the chemical. However, amongst all this data there is seldom any information on fish tissue residues. Occasionally there will be a bioconcentration factor (BCF) study that includes some fish metabolism data but it is not a routine occurrence. Thus, assumptions have to be made which largely attribute any noted toxicity to the parent pesticide

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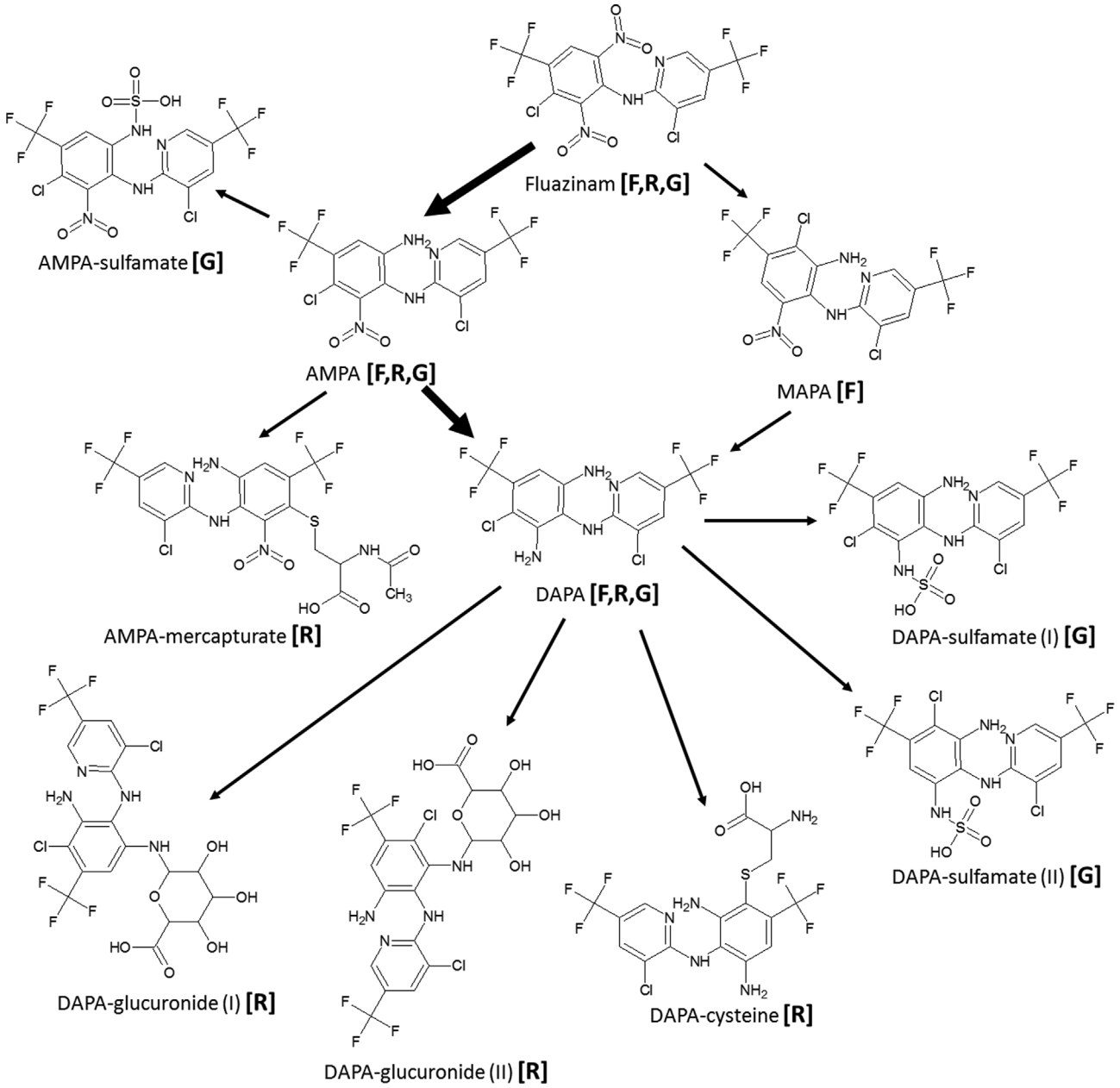

Fig. 1. Overall metabolic map for Fluazinam for Rat (R), Goat (G), and Bluegill fish (F). Thicker arrows indicate major metabolites based on quantitative data.
AMPA = 4-Chloro-6-(3-chloro-5-trifluoromethyl-2-pyridylamino)-α,α,α-trifluoro-5-nitro-m-toluidine
MAPA = 2-Chloro-6-(3-chloro-5-trifluoromethyl-2-pyridylamino)-α,α,α-trifluoro-5-nitro-m-toluidine
DAPA = 4-Chloro-2-(3-chloro-5-trifluoromethyl-2-pyridylamino)-5-trifluoromethyl-m-phenylenediamine.

chemical form, or assume that metabolic pathways measured in a rat study will hold for other species, including fish.

An important part of pesticide chemical risk assessment is the identification of residues of concern. When residues of concern are identified they are based largely on rat metabolism, livestock metabolism residues (typically hen and goat), and/or plant metabolism residue studies. The question of how to use this information to predict potential residues or degradates of concern for environmental species is not often addressed. Thus, extrapolations are often based on very conservative assumptions and/or the use of comparative toxicity Quantitative Structure Activity Relationships (QSARs).

Ingestion of feed containing pesticides by farmed fish can lead to the uptake and occurrence of pesticide residues in fish products. The potential for pesticide residues to be passed through the food-chain to consumers has driven the European Union to publish new data requirements for fish as part of the pesticide approval process (European Union, 2009, 2013a). A working document on the nature of residues in fish has been prepared to provide guidance in conducting fish metabolism studies to quantify and characterize residues which may occur in the edible tissues of fish exposed to pesticides (European Union, 2013b). Following that guidance, Sclechtriem et al. (2016), have developed a standardized testing procedure to study pesticide metabolism by farmed fish in connection with residues in fish feed. As these required studies are eventually submitted in the regulatory process, they too may be used in the comparison of metabolic pathways between fish and other species.

Studying comparative metabolism across species can start to address how well rat metabolism data can predict metabolites (residues) in livestock and in particular in fish where there are very limited data. Assessing the information for representative chemicals across pesticide