Establishing Relationships of Biotransformation Across Organisms

INTRODUCTION

In the CEFIC-LRI funded project Biotransformation Susceptibility of Chemicals in Aquatic Organisms (Eco6) the software 'BiotS' was developed to identify whether a query chemical maybe susceptible to biotransformation/metabolism in aquatic organisms and to provide the user with data on the system(s) in which similar biotransformation has been observed.

The objective of this on-going follow-on project (Eco6.2) is to extend the biotransformation potential of chemicals during fish in-vitro and mammalian in-vivo and in-vitro studies and to investigate the relationships that exist between mammals and other taxa/trophic levels by expanding and improving the previously developed database and software. This approach will help to reduce testing and the use of animals in bioconcentration studies.

METHODS AND RESULTS

Data search for biotransformation pathways of chemicals in fish and mammals

Biotransformation data for chemicals in aquatic organisms that had been collated for the Eco6 project was revisited and data on other aquatic species than fish were removed. A literature search was performed expanding the 186 existing pathways data for fish in-vivo by another 37 (now including pesticides). The data collation for fish (in-vitro) and mammal (in-vitro and in-vivo) biotransformation studies is on-going focusing on the previously identified compounds for the fish in-vivo database.

Data quality scoring system

A system to quality assess the biotransformation data was developed by applying the Klimisch score (Klimisch et al. 1997). Table 1 provides a summary of the quality scores assigned to the fish in-vivo data.

Table 1. Assigned Klimisch quality scores for fish in-vivo experiments

Klimisch score	Number	Percentage
1, Reliable without restriction	1	0.5
2, Reliable with restrictions	122	66.3
3, Not reliable	54	29.3
4, Not assignable	7	3.8
Not relevant [a]	12	-

[a] – category given to experiments used in Eco6 but not currently appropriate to Eco6.2

Susceptible and non-susceptible fragment analysis

Fish in-vivo biotransformation pathway data were analysed so a dataset of 'susceptible' fragments (i.e. molecular fragments that take part in a biotransformation step) as well as 'non-susceptible' fragments (i.e. molecular fragments that do not part in a biotransformation step) was generated. This will be used in the development of the BiotS software v.2.

'CheckMol' software

To aid the fragment analysis, a stand-alone piece of software (CheckMol) has been developed together with systematic fragment identification reasoning. CheckMol allows visualisation of a biotransformation step, identification of the type of step (addition, loss, substitution etc) and identification of the atom number where the biotransformation takes place.

Biotransformation susceptibility weighting score

It is probable that fragments will be identified as both susceptible and non-susceptible to biotransformation in a number of different steps. The number of occurrences a fragment is susceptible and non-susceptible can be used to develop a biotransformation susceptibility weighting score, e.g. weighting score = susceptible score/non-susceptible score, the larger the score the more susceptible a fragment is to biotransformation. This weighting score could be used when examining query molecules in the next version of the BiotS software (see Table 2 as an example of data expected). These tools can then be used to analyse the additional datasets once finalised e.g. mammals and in-vitro fish.

Table 2. Example of expected data and development of susceptibility weighting

Fragment	Non-susceptible score	Susceptible score	Weighting ratio
c1ccccc1	40	2	0.05
c1(ccc(cc1)CCCCCCCC)O	13	21	1.62
C(O)=O	3	24	8.00
c1ccc2c(c1)[nH]c(n2)NC(OC)=O	11	12	1.09

BiotS

BiotS v.2.0 will be developed as a standalone desktop application with a graphical user interface in the programming language Java. The software will allow the user to enter the structure of a query molecule using smiles notation and then search for the presence of susceptible and non-susceptible fragments. If fragments are identified the user can access information on:

- the location of the fragment in the molecule
- in which species (mammals, fish) biotransformation has been observed
- the studies where the fragments have been observed biotransforming e.g. exposure duration, concentration, analytical specifications
- biotransformation rate
- differences and similarities on e.g. metabolic pathways if fragments have been identified to biotransform in more than one species

This project is on-going and will be due for completion in March 2010.

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