Use of QSARs to Promote More Cost-Effective Use of Chemical Monitoring Resources.

1. Screening Industrial Chemicals and Pesticides, Direct Food Additives, Indirect Food Additives and Pharmaceuticals for Biodegradation, Bioconcentration and Aquatic Toxicity Potential

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Monitoring studies are expensive to conduct. To promote more cost-effective use of chemical monitoring resources, quantitative structure activity relationships (QSARs) are proposed as methods to identify chemicals that could be found in, and cause adverse effects to, organisms in water, sediment and soil from the Great Lakes basin. QSARs were used to predict the biodegradation, bioconcentration and aquatic toxicity potential of 2697 industrial chemicals and pesticides, 1146 direct food additives, 967 indirect food additives and 282 pharmaceuticals that could be released to the Great Lakes basin. The QSARs identified 47 industrial chemicals and pesticides, 20 direct food additives, 13 indirect food additives and 7 pharmaceuticals with bioconcentration or aquatic toxicity potential or potential to not biodegrade readily. Most of these chemicals were predicted to partition to sediments. Using QSARs to identify chemicals with potential to persist, bioconcentrate or partition to sediments will promote more cost-effective use of chemical monitoring resources by allowing researchers to focus their analytical techniques on measuring chemicals predicted to persist in water or soil, bioconcentrate in fish or partition to sediments so that the effects of these chemicals can be assessed on indigenous organisms.

Key words: QSARs, monitoring, chemical testing, saving resources

Introduction

The Great Lakes Water Quality Agreement commits the United States and Canada to restore and protect the chemical integrity of the Great Lakes basin. In particular, the Agreement commits to “virtually eliminate” selected persistent toxic substances. While progress has been made reducing these substances in the Great Lakes basin, other chemicals are emerging as potential pollutants in the basin. Given the thousands of industrial chemicals, pesticides, pharmaceuticals, food additives and other substances that could be contaminating the Great Lakes, it is proposed that quantitative structure activity relationships (QSARs) be used to identify these emerging pollutants that are likely to cause adverse effects to organisms in water, sediment and soil from the Great Lakes basin.

Previously, QSARs have been applied to identify many untested chemicals for more intensive and costly experimental evaluations (Walker and Brink 1989; Walker 1991, 1995a). These applications of QSARs have promoted more cost-effective use of testing resources (Walker 1995b; Walker et al. 2003). However, to our knowledge, QSARs have not been used to identify chemicals on which environmental or occupational monitoring could be based. The purpose of this paper is to illustrate how QSARs can be used to identify substances that could be contaminating the Great Lakes and to illustrate how the use of QSARs can promote more cost-effective use of Great Lakes chemical monitoring resources.

Methods

Four lists of chemicals maintained by the Toxic Substances Control Act (TSCA) Interagency Testing Committee (ITC) were used to evaluate the biodegradation, bioconcentration and aquatic toxicity potential of chemicals that could be released into the Great Lakes. The lists consisted of industrial chemicals and pesticides, direct food additives, indirect food additives and pharmaceuticals. Previously described methods used by the ITC during implementation of the Degradation Effects Biocon-
centration Information Testing Strategies (DEBITS) were used to screen these chemical substances for biodegradation, bioconcentration and aquatic toxicity potential (Walker and Carlsen 2002; Carlsen and Walker 2003).

DEBITS biodegradation factors (BCFs) were predicted using the BCFWIN program from the Syracuse Research Corporation EPI Suite of estimation programs. BCFs were estimated from the octanol-water partition coefficients and a series of structural correction factors (Meylan et al. 1999). BCFWIN is available on the U.S. EPA’s web site (http://www.epa.gov/opptintr/exposure/docs/episuite.htm). BCFs of >1000 and >5000 have been used by the U.S. EPA (1999) to screen chemicals for bioconcentration potential. Chemicals with BCFs >1000, but <5000 were assigned a medium bioconcentration potential. Chemicals with BCFs >5000 were assigned a high bioconcentration potential.

DEBITS biodegradation predictions were obtained by using the BIOWIN program from the Syracuse Research Corporation EPI Suite of estimation programs (http://www.epa.gov/opptintr/exposure/docs/episuite.htm). The ultimate aerobic biodegradation probabilities (BDPs) from the ultimate survey model in BIOWIN were used to predict persistence potential. These predictions were based on expert opinions that different structural groups could be used to estimate a chemical’s biodegradation potential (Boethling et al. 1994). The ITC used BDPs of <2 and ≤1.75, because chemicals with these BDPs were likely to persist for approximately 2 and 6 months, respectively. Chemicals with BDPs <2 are associated with a medium persistence potential. Chemicals with BDPs <1.75 were assigned a high persistence potential.

Aquatic toxicity predictions were made using the U.S. EPA’s ECOlogical Structure Activity Relationship (ECOSAR) model. ECOSAR reflects how the U.S. EPA predicts the aquatic toxicity of new chemicals under TSCA section 5. ECOSAR is based on 2-dimensional chemical structures and modes of action. The latest version of ECOSAR is available on the web (www.epa.gov/oppt/exposure/docs/episuite.htm). ECOSAR has been used to predict the aquatic toxicity of hundreds of new chemicals (Clements et al. 1993; Cash 1998).

These predictive QSAR models were incorporated into the U.S. EPA’s PBT Profiler that has been previously described and compared to DEBITS (Walker and Carlsen 2002). The BIOWIN ultimate survey model that is used in the Profiler assumes aerobic conditions, but deeper layers of aquatic sediments are usually anaerobic. To account for the lower rate of ultimate biodegradation in sediment, the PBT Profiler uses a multiplier of 9, e.g., chemicals with half-lives of 60 or 180 days in water would have half-lives of 540 or 1620 days in sediment, respectively. The PBT Profiler also makes an adjustment for the biodegradation rate for soil by using a multiplier of 2, e.g., chemicals with half-lives of 60 or 120 days in water would have half-lives of 120 or 240 days in soil, respectively. The PBT Profiler assigns persistence to chemicals based on the amount expected to be found in water, soil, and sediment as determined by a level III multimedia mass balance model (Mackay et al. 1992). It then determines to which of these three compartments the chemical is most likely to partition (the one with the highest percentage) and assigns the persistence based on the half-life in this predominant compartment. The PBT Profiler assigns high persistence to chemicals with half-lives in the predominant compartment of >180 days. Chemicals with a half-life in the predominant compartment of ≥60 and ≤180 days were assigned medium persistence potential.

Results

The QSAR models described above were used to screen 2697 industrial chemicals and pesticides, 1146 direct food additives, 967 indirect food additives and 282 pharmaceuticals for biodegradation, bioconcentration and aquatic toxicity potential. As a result 47 industrial chemicals and pesticides, 20 direct food additives, 13 indirect food additives and 7 pharmaceuticals were identified that had bioconcentration or aquatic toxicity potential or potential to not biodegrade readily (Table 1).

All 87 of the industrial chemicals and pesticides, direct food additives, indirect food additives and pharmaceuticals with bioconcentration or aquatic toxicity potential or potential to not biodegrade readily had predicted fish acute toxicity values <1 mg/L (Table 1). Most also had BCFs >5000, except for 1 direct food additive, 3 indirect food additives and 5 pharmaceuticals (Table 1). Only the industrial chemicals and indirect food additives included chemicals with predicted persistence half-lives of 1620 days, similar to Mirex (Fig. 1 and 3). The direct food additives and pharmaceuticals included chemicals with predicted persistence half-lives of 340 and 540 days similar to chlordane, hexachlorobenzene and toxaphene (Fig. 2 and 4). Sediment was the predicted predominant compartment for most of the industrial chemicals and pesticides, direct food additives, indirect food additives and pharmaceuticals, except for 4 industrial chemicals and 3 pharmaceuticals with predicted persistence of 360 days and 1 pharmaceutical with a predicted persistence of 120 days (Table 1).

Discussion

The Great Lakes Advisory Board of the International Joint Commission (IJC) was one of the first organizations to sponsor a symposium on structure activity relationships (Veith and Konasewich 1975). As a result the IJC had an early opportunity to consider the potential of QSARs to predict the biodegradation, bioconcentration and aquatic toxicity potential of chemicals of concern to the Great
Lakes. Since that 1975 symposium numerous QSARs have been developed to predict the biodegradation, bioconcentration and aquatic toxicity potential of chemicals.

As noted above, the BIOWIN QSARs that were used to predict the biodegradation of the industrial chemicals and pesticides, direct food additives, indirect food additives and pharmaceuticals were based on potential aerobic biodegradation and corrected for potential anaerobic biodegradation if soil or sediment was the predicted predominant compartment. While these predictions probably account for most persistence, it is possible that some of these chemicals are susceptible

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>#</th>
<th>Predominant compartment</th>
<th>Persistence (days)</th>
<th>BCF</th>
<th>Aquatic toxicity (mg/L)</th>
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<td>23</td>
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<td>Total</td>
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</table>

Fig. 1. Predicted biodegradation, bioconcentration and aquatic toxicity potential of industrial chemicals compared to known persistent bioaccumulative toxicants (PBTs).

Fig. 2. Predicted biodegradation, bioconcentration and aquatic toxicity potential of direct food additives compared to known persistent bioaccumulative toxicants (PBTs).
to hydrolysis or volatilization. Hydrolysis half-lives and Henry’s Law constants of these chemicals have been evaluated (Walker et al. 2004).

The ECOSAR model that was used to predict the aquatic toxicity potential of the industrial chemicals and pesticides, direct food additives, indirect food additives and pharmaceutical chemicals relies on different linear regression equations for each chemical class, that mostly relate toxicity to a chemical’s octanol-water partition coefficient (Kaiser et al. 1999). As noted by Moore et al. (2003), this approach generally works well for chemicals that exert their toxicity through general membrane disruption, e.g., through non-polar narcosis mode of action. For these substances, toxicity is a function of the tendency to dissolve in chemical membranes, which in turn is related to the octanol-water partition coefficient (Nowsome et al. 1984; Hodson et al. 1988). Hermens et al. (1985), Fiedler et al. (1990) and de Bruijn and Hermens (1991) suggested that this approach may be problematic for chemicals for which the mode of toxic action is uncertain or highly specific. Additional studies of the industrial chemicals and pesticides, direct food additives, indirect food additives and pharmaceuticals were conducted to predict modes of toxic action (Walker et al. 2004).

The BCFWIN model that was used to predict the bioconcentration potential of the industrial chemicals and pesticides, direct food additives, indirect food additives and pharmaceuticals is based on octanol-water partition coefficients and a series of structural correction factors (Meylan et al. 1999). More recent methods developed by Dimitrov et al. (2002a,b, 2003) have re-evaluated the criteria that influence bioavailability and hence BCFs. The analysis of the molecular minimum, effective and maximum cross-sectional diameters of energetically reasonable conformers revealed that these geometric characteristics are strongly dependent on molecular flexibility (Dimitrov et al. 2002a,b, 2003). The complexity of the effect of molecular flexibility on molecular size and subsequently on bioavailability and BCFs was evaluated for the 47 industrial chemicals and pesticides, 20 direct food additives, 13 indirect food additives and 7 pharmaceuticals (Walker et al. 2004).

Conclusions

QSARs were used to predict the biodegradation, bioconcentration and aquatic toxicity potential of 2697 industrial chemicals and pesticides, 1146 direct food additives, 967 indirect food additives and 282 pharmaceuticals that could be released to the Great Lakes basin. Forty-seven (47) industrial chemicals and pesticides, 20 direct food additives, 13 indirect food additives and 7 pharmaceuticals were identified that had bioconcentration or aquatic toxicity potential or potential to not biodegrade readily.

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or any of the U.S. government organizations represented on the ITC, including the U.S. EPA.

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