The Use of Quantitative Structure-Activity Relationships (QSARs) in Fate and Risk Assessment of Persistent Organic Pollutants (POPs)

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Introduction

The number of existing chemicals is large and it can be expected that a substantial number of these in one way or another will end up in the environment. The variation in chemical structures and complexity in environmental processes, is almost infinite. To test all potentially hazardous compounds is neither economically nor experimentally feasible. In this situation there is a need of predictive tools which as accurate as possible estimate the fate and effects of large numbers of substances which have not yet been investigated. The estimation of environmental behaviour of persistent organic pollutants (POPs) can be based on the general assumption that a change in chemical structure will correspond to a change in environmental fate or toxicological activity. This relation between chemical structure and activity (property) can be expressed in quantitative structure-activity (property) relationships, so-called QSARs (QSPRs). The increased knowledge of the environmental and toxicological effects seen for several groups of POPs and the large number of individual substances with suspected persistent properties have introduced the QSAR approach into the fields of environmental chemistry and toxicology. Today, QSAR techniques is established as an important tools in fate and risk assessment of environmentally active compounds (1).

POPs consist of a multitude of individual compounds, e.g. the polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), biphenyls (PCBs), and naphthalenes (PCNs) are theoretically as many as 494 different compounds. Thus, in order to understand the environmental fate and biological effects of such groups of compounds, a detailed physico-chemical characterisation is needed in order to capture the chemical factors of importance. The physico-chemical characterisation will thus be multivariate if the many facets of chemical structure are to be described. It is expected that such a broad chemical characterisation will capture the underlying, hidden factors that correlate with the response of interest.

The aim of this paper is to present a strategy for the development and use of QSARs for POPs. The complexity in the physico-chemical properties as well as biological activity is illustrated by using the PCBs as an example.

Methodology

One main objective in the establishment and use of QSARs in fate and risk assessment of POPs is to develop models with high predictive power, i.e. QSAR models which generate reliable estimates of the activity under investigation (2). In many cases QSARs are applied as an additional step in the evaluation of existing data, i.e. the QSARs was not the primary objective in the study. In these models, predictions can only be made in a narrow range of chemical structures and thus the use of the calculated QSARs as predictive tool will be of limited value. However, if the data is generated from a systematic QSAR approach, including a designed selection procedure, the predictive capability can increase and cover the whole class of compounds under investigation (3). Figure 1 describes a general approach for the development QSARs for POPs.

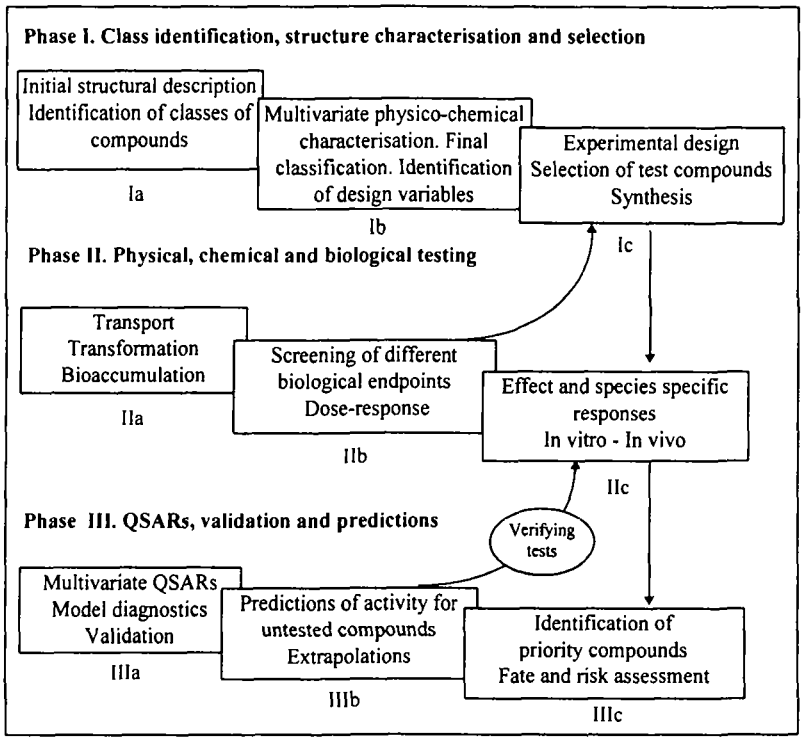

Figure 1. General approach for the development of QSARs for POPs.

As can be seen in Figure 1, the strategy is divided in three phases. Notable is that the QSAR calculations appear in the last phase. The initial part, including the physico-chemical characterisation and systematic selection of test compounds is crucial for outcome of the QSARs and if the models can generate information of the whole class. The different phases of the strategy are illustrated by the PCB example below.

Illustration of the strategy: Polychlorinated biphenyls (PCBs)

Phase I. Class identification, structure characterisation and selection. The PCBs consist of 209 different congeners with varying degree of chlorination and substitution pattern. The class of compounds is easy to identify, however the first step (see Ia in Figure 1) in this phase might be to limit the investigation to a sub-group of PCBs. In this example, the 154 tetra- to heptachlorinated congeners were selected, hence the most biologically active compounds can be expected to be find among these homologue groups. The second step in phase I was to perform a multivariate physcio-chemical characterisation of the 154 PCBs. All together, 52 physico-chemical variables (4,5,6) were generated and summarised by using principal component analysis (PCA). A 2^4-factorial design was used to select a set of 16 congeners which represented the whole chemical domain of the tetra- to heptachlorinated PCBs (7). Additional 4 congeners were selected to provide information about the interior region of the class of PCBs.

Phase II. Physical, chemical and biological testing. The second phase of the strategy includes a broad spectra of testing possibilities. Different test systems considered to be important for the assessment of PCBs have been included. The PCBs were tested regarding abiotic transformation/stability as well as several biological responses. A summary of the different studies is given in Table 1. Thermal and photolytic stability were investigated and structure-dependent dechlorination and transformation were identified. All *in vitro* and *in vivo* systems investigated have shown relationships between chemical structure and biological activity.

Table 1. Summary of test systems (phase II) and QSAR models (phase III).

Test systems (Phase II)	Results (Phase III)
Thermal and photolytic transformation (8,9)	Structure dependent dechlorination pathways were found for thermal and photolytic transformation, however different dechlorination products are identified in the two systems.
Bioaccumulation and bio-magnification in sticklebacks (10), zebra fish (11), arctic char (12) and earthworms (13)	*In vivo* screening of the bioaccumulation (magnification) potential in different species. QSARs predict bioaccumulation and biomagnification potential for large numbers of PCBs.
EROD & MROD induction in monkey , pig, and chicken hepatocytes (14,15,16)	*In vitro* screening of Ah-receptor mediated biochemical responses in different species. QSARs predict approx. 30 PCBs as high priority compounds with dioxin-like properties.
Porphyrin accumulation in chicken hepatocytes (15)	*In vitro* screening of effects on the heme synthesis. The majority of the tetra-to heptaCBs were found to be active.
Cell-cell communication inhibition (17)	*In vitro* screening of intercellular communication inhibition. QSARs predict a large number of multiple-ortho substituted PCBs as highly potent.
Reproduction effects in zebrafish (18,19)	*In vivo* screening of reproductive effects for selected PCBs. A complex effect pattern was identified showing effects of non- as well as multiple ortho substituted PCBs.

Phase III. QSARs, validation and predictions. Based on the results from phase II, quantitative structure-activity relationships (QSARs) were calculated in order to define the correlation between the chemical properties and biological activity. Validated QSAR models were

capable of predicting the activity (abiotic and biological) of all non tested PCBs and thus ranking all 154 tetra-to hepta-chlorinated PCBs.

The systematic selection approach in combination with QSAR presented in this paper is a useful tool in the screening of different effects caused by persistent organic compounds. The chemical properties connected with a certain biological effect can be characterised and sub-groups of compounds identified on which test resources should be focused. The presented method has so far mainly focused on dioxin-like responses and the methodology has been used in a recent re-evaluation of toxic equivalency factors (TEFs) for humans and wildlife (20). The presented approach is suggested to be used in the screening of other effects, such as neurotoxicity and effects on reproduction and endocrine system, also including other groups of persistent organic pollutants.

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