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AN OVERVIEW OF THE USE OF QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIPS FOR RANKING AND PRIORITIZING LARGE CHEMICAL INVENTORIES FOR ENVIRONMENTAL RISK ASSESSMENTS

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Abstract—Ecological risk assessments for chemical stressors are used to establish linkages between likely exposure concentrations and adverse effects to ecological receptors. At times, it is useful to conduct screening risk assessments to assist in prioritizing or ranking chemicals on the basis of potential hazard and exposure assessment parameters. Ranking of large chemical inventories can provide evidence for focusing research and/or cleanup efforts on specific chemicals of concern. Because of financial and time constraints, data gaps exist, and the risk assessor is left with decisions on which models to use to estimate the parameter of concern. In this review, several methods are presented for using quantitative structure–activity relationships (QSARs) in conducting hazard screening or screening-level risk assessments. The ranking methods described include those related to current regulatory issues associated with chemical inventories from Canada, Europe, and the United States and an example of a screening-level risk assessment conducted on chemicals associated with a watershed in the midwest region of the United States.

Keywords—Chemical ranking Chemical screening Regulation Chemical inventory Risk assessment

INTRODUCTION

Various governmental entities, including Environment Canada, the European Union (EU), and the U.S. Environmental Protection Agency (U.S. EPA), utilize ecological risk assessments to evaluate the potential adverse effects that exposure to a single chemical or combination of chemicals will have on an ecosystem. The basic framework for conducting ecological risk assessments, as outlined by the U.S. EPA, is divided into three components: problem formulation, analysis, and risk characterization [1]. The first two elements of the risk assessment require data acquisition to assist in the characterization of the effects and exposure associated with the stressor. A major issue leading to uncertainty in risk assessments is the lack of reliable data.

For risk assessments addressing a limited number of chemicals, data generation may be appropriate and cost effective, but in cases where large inventories of chemicals need to be screened, data generation is not feasible because of fiscal and time constraints. For instance, under the Toxic Substances Control Act (TSCA), the TSCA Interagency Testing Committee (ITC) is required to screen existing chemicals, prioritizing those chemicals that pose an unreasonable risk to human health or the environment and adding them to the TSCA Section 4(e) priority testing list in May and November reports to the U.S. EPA Administrator [2,3]. The TSCA list of existing chemicals includes more than 12,000 discrete organic chemicals with significant production volumes and little or no effects and exposure data [4]. The TSCA also requires that the 2,300 chemicals per year submitted under the premanufacture notification (PMN) program be reviewed for potential hazard to human health and the environment, but approximately 95% of the submissions include no ecotoxicity data [5]. Canada and Europe have similar programs. The Canadian Environmental Protection Act (CEPA) requires Environment Canada and Health Canada to categorize the domestic substances list (DSL), which is comprised of approximately 23,000 substances, on the basis of properties such as persistence, bioaccumulation, and inherent toxicity [6,7]. The European inventory of existing commercial substances (EINECS), which includes more 100,195 existing chemicals, must undergo a systematic evaluation in relation to potential hazard [8].

In addressing large inventories, risk assessors have developed tools for ranking chemicals on the basis of both exposure and effects. These screening tools usually take a tiered approach, first using empirical data obtained from databases that have been verified for data quality and supplementing data gaps with estimated values generated from quantitative structure–activity relationships (QSARs). To minimize uncertainties associated with hazard screening or a screening-level risk assessment, the empirical data should use well-defined endpoints generated using reliable and approved test protocols. In addition, the species should be relatively sensitive. To minimize uncertainties, QSARs should be developed using rigorous data and developed and applied on the basis of the underlying process or mechanism of action of the chemical in relation to the biological receptor [1,9].

This review describes various tools that utilize QSARs for screening large chemical inventories and the application of one ranking tool in assessing pesticides found in a midwestern U.S. watershed. The tools evaluated in this exercise, for the most part, follow proposed guidelines for conducting chemical

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prioritization and ranking [10]. A summary of how the effects and exposures are characterized within the screening tools are presented. The chemical inventories will be described, along with sources of high-quality data used in the ranking exercises, and an overview of the application of QSARs in screening-level risk assessments is given.

Because the focus of this paper is the use of QSARs in screening large chemical data sets, it is important to note that certain chemical groups that may be regulated by governmental agencies will not be considered in this review because of limitations with the associated QSAR models for these compounds (e.g., polymers, metals). It is also important to note that structure–activity relationships utilize information on discrete chemical structures; therefore, chemical mixtures are excluded from this type of analysis.

Uncertainties are associated with any QSAR model. The test methods used, quality of the empirical data used in model development, diversity of chemical structures, and number of chemicals representing various endpoint categories can all affect the usefulness of QSARs. These prioritization and screening tools all require some professional judgment, and users should ensure that the models are appropriately applied. Also, readers should be aware that this paper is presenting models based on their use in current ranking and screening tools. Readers are referred to other papers within this review issue for a more complete synopsis of available QSAR models for estimating environmental effects and exposure parameters.

CHEMICAL INVENTORIES AND REGULATORY REQUIREMENTS

Various regulatory actions have been promulgated to address the manufacturing and release of chemicals into the environment. It is estimated that more than 120,000 chemicals are manufactured worldwide [11]. This review addresses three inventories of existing chemicals regulated by governmental agencies: Canada's DSL, the EU's EINECS, and the U.S. EPA's TSCA Inventory. In assessing the potential risk associated with the release of these chemicals into the environment, risk assessors must evaluate the effects and exposure to humans and ecological receptors. In an analysis of hazard assessment information available for chemicals in commerce within the United States, more than 78% of the chemicals lacked human health toxicity data [12]. Similarly, approximately 95% of new PMN notices submitted to the U.S. EPA do not include any ecotoxicology data [5]. Therefore, regulators are faced with the task of reviewing the potential risk for chemicals having little or no empirical data.

Canadian DSL

The DSL is a list of substances that were in Canadian commerce between January 1, 1984, and December 31, 1986, and were used for manufacturing purposes or manufactured in or imported into Canada in a quantity of 100 kg or more in any calendar year. The list has been amended from time to time to include eligible substances notified under the New Substances Notification Regulations and currently contains approximately 23,000 substances. Types of substances on the DSL include simple organic chemicals, pigments, organometallic compounds, surfactants, polymers, metal elements, metal salts and other inorganic substances, and substances that are of ''Unknown or variable composition, complex reaction products, or biological materials'' (referred to as UVCBs) [7].

The CEPA requires Environment Canada and Health Canada to categorize and then, if necessary, conduct a screening-level risk assessment on substances listed on the DSL to determine whether they are toxic as defined in the regulation [6,7]. Under CEPA, a substance is defined as toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or it constitutes or may constitute a danger to human life, health, or the environment on which life depends. The CEPA requires that all substances on the DSL be categorized by 2006. This categorization phase will identify chemicals that are persistent (P) or bioaccumulative (B) and inherently toxic (iT). Substances identified as PiT, BiT, or PBiT are subjected to a screening-level risk assessment where the level of potential risk is determined. The outcome of a screening-level risk assessment is either no further action, recommend addition of the substance to the list of toxic substances under CEPA, or add to the Priority Substances List in order to assess more comprehensively the risks associated with the release of the substance.

Environment Canada organized an international workshop in November 1999 in Philadelphia (Pennsylvania, USA) to determine the state of the science on estimating persistence, bioaccumulation, and ecotoxicity. The objective also included a discussion of the selection, application, and interpretation of the QSARs to categorize the substances. A workshop proceedings is available [13]. The proceedings is being used to develop a guidance document for the categorization of organic substances on the DSL.

EINECS

The EINECS is the European Commission's inventory of 100,195 chemical substances that were reported by the member states as existing on the European Community Market before September 18, 1991 [8]. The EINECS was developed by the European Commission in response to Article 13 of Directive 67/548 (see [14] for a summary of European Community regulations.) EINECS does not include synthetic polymers (the monomeric unit appears on EINECS), intentional mixtures, food and feedstuffs, medical and cosmetic products, pesticides, and alloys [15]. Under Council Regulation 793/93, industry must provide information for substances produced or manufactured in quantities of more than 1,000 metric tons/year. These substances are referred to as the high production volume chemicals (HPVCs). For these HPVCs, industry must submit the name of the substance, amount produced and/or imported, classification or labeling as directed under 67/548, and uses of substance. If available, industry must also provide any physical/chemical property information, data on fate and transport, and toxicity and ecotoxicity data. All data submissions are transferred into the International Uniform Chemical Database (IUCLID) system, and excluding confidential business information, the database is available to the public. The IUCLID system will be used in setting priorities through preliminary risk assessments. Eventually, on the basis of more rigorous risk assessments, the Commission could ban or restrict the use of a substance that poses a substantial risk.

The EU's HPVC list includes more than 2,600 substances as of October 2000 (http://ecb.jrc.it/existing-chemicals), representing a range of chemical classes that includes discrete organic chemicals (~47%), inorganic substances (~14%), petroleum-based products (~16%), UVCBs (~11%), chemical mixtures (~9%), and organometallic substances (~1%) [15].

An analysis of the data submissions from industry on these substances [15] identified significant data gaps, with 21% of the chemical submissions not including any supplementary data (physical/chemical properties, chemical fate and transport, or toxicity and ecotoxicity values). For industrial organic chemicals, only 54% of the chemicals had any ecotoxicity data submitted.

U.S. EPA's TSCA Inventory

Under Section 8 of the U.S. EPA's TSCA, promulgated in 1976, an inventory of chemicals in commerce was developed, excluding drugs, pesticides, tobacco, food products and additives, and radioactive materials (Public Law 94-469). In 1976, 61,000 chemicals were in commerce [2,16], but since that time, more than 10,000 substances have been added to the inventory based on PMN reviews [5]. Currently, the TSCA Inventory contains about 75,000 chemical substances, including approximately 30,000 polymers and complex mixtures [17].

The U.S. EPA classifies chemicals in commerce into two main categories: existing and new. Existing substances are those already on the TSCA Inventory. Under Section 4 of TSCA, Congress created the ITC, an independent advisory committee to the U.S. EPA Administrator, with the responsibility to rank and prioritize existing chemicals for testing on the basis of suspicion of toxicity in the absence of data and to add these chemicals to the ITC's priority testing list. The ITC's priority testing list is revised and submitted as a report to the U.S. EPA Administrator every May and November. The Administrator may then recommend that the manufacturers of these chemicals provide data to better document the potential exposure or hazard associated with a substance (for a more complete summary of the ITC process, see [2,17].) The ITC has developed and used numerous procedures to screen over 45,000 chemicals on the TSCA Inventory [2,16–30]. New chemicals are addressed under Section 5 of TSCA, which requires manufacturers to submit information on the chemical structure/identity, production volume, by-products, intended use, environmental release, disposal practices, and human exposure levels. Manufacturers are also required to submit any available toxicity data. The U.S. EPA must evaluate the potential risk associated with these new chemicals within 90 d using the information provided in the PMN (for a more complete summary of the PMN process, see [31]).

PRIORITIZATION AND RANKING PROTOCOLS

Initial screening based on production volume

The EU has focused initial screening efforts on HPVCs, defined as substances produced in excess of 1,000 metric tons/year. The HPVC list reduces the focus from the complete EINECS data set of over 100,000 chemicals to approximately 2,600 substances. Similarly, the U.S. EPA Administrator can require testing of a substance if it is produced in substantial quantities or is anticipated to be released into the environment in reasonable quantities under Section 4(a) of the TSCA. The U.S. EPA's ITC uses a cutoff of >10,000 lb/year, with more than 12,500 of the TSCA chemicals meeting this criterion [2]. The ITC has further identified nearly 4,000 compounds on the TSCA Inventory that are either HPVCs, defined as produced or imported in volumes between 1 million and 1 billion lb/year, or very HPVC, defined as substances produced or imported in volumes exceeding 1 billion lb/year. The U.S. EPA's HPV challenge program is addressing HPVCs and very HPVCs (http://www.epa.gov/opptintr/chemrtk/volchall.htm).

Table 1. Canadian Environmental Protection Act criteria for persistence and bioaccumulation [13]

Persistence[a]		
Media	Half-life[b]	Bioaccumulation[c]
Air	≥2 days[d]	BAF ≥5,000 or
Water	≥6 months	BCF ≥5,000
Sediment	≥1 year	or
Soil	≥6 months	log K_{ow} ≥5

[a] A substance is considered persistent when the criterion is met in any one medium.
[b] The time it takes for half of the amount of a substance to be transformed in a medium.
[c] Bioaccumulation factors (BAF) are preferred over bioconcentration factors (BCF); in the absence of BAF or BCF data, the octanol–water partition coefficient (log K_{ow}) may be used.
[d] A substance may be considered as persistent in air if it is shown to be subject to atmospheric transport to remote regions such as the Arctic.

Even this initial screen leaves risk assessors with a daunting task when evaluating the potential effects and exposure of thousands of chemicals because of significant data gaps in existing empirical databases and quality concerns on data that are available. For this reason, screening rules are defined to identify priority pollutants for testing or further review.

CEPA: Proposed categorization and screening approach

As mentioned previously, in Canada CEPA requires that each substance on the DSL go through a categorization step based on its potential to persist (P) in the environment or its ability to bioaccumulate (B) and its inherent toxicity (iT). If a substance is identified as PiT, BiT, or PBiT, the substance must then undergo a screening-level risk assessment. For each parameter, criteria are identified, and, if exceeded, the substance is labeled as either persistent, bioaccumulative, or inherently toxic. Transformation half-lives are used to characterize persistence, and either the bioaccumulation factor (BAF), bioconcentration factor (BCF), or octanol–water partition coefficient (log K_{ow}) is used to characterize bioaccumulation (Table 1). Under CEPA, criteria for persistence and bioaccumulation are specified in the Persistent and Bioaccumulation Regulation and are consistent with the Toxic Substances Management Policy [13,32]. A persistent substance is defined as having a half-life of ≥6 months for water or soil, ≥2 d in the air, or ≥1 year in the sediment. If a substance meets any of these half-life threshold values, it is determined to be persistent. A substance may also be determined to be persistent in air if it is shown to be subject to atmospheric transport to remote regions such as the Arctic. In defining bioaccumulation, BAF values are preferentially selected over BCF values, and BCF values are preferentially used over log K_{ow} values. A substance is bioaccumulative if it has a BAF ≥5,000 or a BCF ≥5,000 or a log K_{ow} ≥5. Environment Canada will rely on models to estimate these parameters. The reliability of QSARs for making log K_{ow} and persistence predictions has been assessed [33].

The CEPA does not provide a definition for inherently toxic, nor does it provide criteria. Environment Canada has proposed a definition and criteria for iT to nonhumans that are currently being refined within a technical advisory group and Environ-

ment Canada. Categorization of substances as inherently toxic on the DSL will be based on both aquatic and terrestrial species. Environment Canada expects that for most substances, the categorization based on inherent toxicity will be driven mainly by aquatic endpoints, which encompass most of the available ecotoxicity data. The exception will be substances with high log K_{ow} values, where endpoints for non–water column biota may become more important because of food chain transfer.

European Risk Ranking Method

The EU Risk Ranking Method (EURAM) is used to prioritize substances on EINECS for further review of potential risk [8]. This is a ranking system and does not use threshold values but rather places each chemical in rank order on the basis of scores received for environmental exposure and toxicity and human health exposure and toxicity. This chemical ranking is then used to select a list of priority pollutants for a more rigorous risk assessment. As mentioned previously, initial prioritization of the EINECS selected HPVCs for further evaluation. Using the EURAM, empirically derived data are selected from the IUCLID system, and when data gaps exist, QSAR-predicted values are used [34,35]. Within EURAM, separate scores for exposure and effects are calculated, and the scaled ratios of the exposure and effects scores are used to obtain a final environmental score. Based on guidance documents, the environmental risk assessments should address the protection of aquatic and terrestrial ecosystems, top predators, the atmosphere, and microorganisms in sewage treatment plants [35]. Because of the greater availability of aquatic-based QSAR models and aquatic organism data in the IUCLID system, the EURAM bases potential risk on aquatic ecosystems and ignores the other components. Under Council Directive 67/548, manufacturers are required to submit results of a 96-h fish mortality study median lethal concentration (LC50), a 48-h *Daphnia* immobilization study median effective concentration (EC50), a 72-h algal growth inhibition study (IC50), and a bacterial respiration inhibition study for use in biodegradation assessments. These data are included in IUCLID. If a sufficient amount of quality test data and/or reliable models become available for the nonaquatic components, these compartments will be incorporated into later assessments.

The EURAM's exposure ranking is based on three parameters: the amount of substance to which humans or the environment could potentially be exposed based on estimation techniques, the distribution of the substance into various environmental compartments, and the potential of the chemical to degrade once it has been released into the environment [8]. Using an algorithm, these parameters are used to estimate the environmental exposure value or predicted environmental concentration (PEC). The resulting PEC values are scaled between 0 and 10 to obtain the final exposure score for a particular environmental compartment. An exposure score is also developed for top predators by multiplying the PEC for the aquatic compartment by a scaled version of the BCF, which ensures that the top predator value does not contribute more weight than the other environmental compartments to the final ranking. If BCFs are not available, a scaling of log K_{ow} is used to define the accumulation potential for the top predators [8].

When calculating environmental effects scores, chronic no-observable-effect concentration (NOEC) values are preferentially selected from IUCLID over acute values if both are available for a particular species. If chronic NOECs are available for one or more species, then these values are used in deriving the predicted no-effect concentration (PNEC) for each compartment; otherwise, the acute values are used. The lowest toxicity values are used in deriving the PNEC (either the lowest NOEC or the lowest LC50 or EC50 value). Assessment factors are used, with the magnitude of the assessment factors determined by the duration of the study (chronic vs acute) and the number of species with data available for the selected endpoint. The final effect score is generated by normalizing the PNEC to values between 0 and 10. The final environmental score (range 0–100) is the environmental exposure score multiplied by the environmental effects score. For more details on the methods used in the EURAM model and calculating of PEC and PNEC, see [8,34,35].

ITC prioritization approach for testing recommendations

The U.S. EPA's ITC has adopted a tiered approach for use in prioritizing the selection of chemicals for consideration of testing recommendations. As previously mentioned, initial prioritization of substances on the TSCA Inventory are those manufactured in quantities ≥10,000 lb/year. In the next step, characterizing potential exposure, chemicals are selected for further review using a tiered set of threshold values for hydrolysis half-life (>1 d), Henry's law constant ($<10^{-2}$ atm m^3/mole), log K_{ow} (>4), aerobic and anaerobic biodegradation (≥1 week), and molecular cross section of the chemical (<9 Å) [17]. This integrated approach allows the ITC to focus testing recommendations on chemicals that are more persistent in the environment. The ITC has supplemented this assessment using the Degradation Effects Bioconcentration Information Testing Strategies system to identify substances on the TSCA Inventory that have the potential to persist and bioconcentrate [4]. Under this system, the TSCA Inventory is organized by production volume. Within production volume classes, substances with log K_{ow} values between three and six, a probability of biodegradation <2 based on Syracuse Research (Syracuse, NY, USA) (SRCs) biodegradation probability program (BIOWIN), and BCF values >1,000 are flagged as chemicals of concern [4]. The initial screening of 12,557 discrete organic chemicals with production volumes exceeding 10,000 lb identified 80 substances that met all these requirements.

Subsequent to the screening based on environmental exposure, the ITC also compares existing and modeled aquatic toxicity values to PECs and various threshold values. To derive PECs, the ITC used the Probabilistic Dilution Model [36]. Occasionally, the ITC uses the Exposure Analysis Modeling System to provide additional environmental fate estimates [37]. For acute studies, the chemical is given a higher priority in the screening if the substance demonstrates a potential to cause cumulative toxicity and the LC50 or EC50 ≤(100·PEC), the LC50 or EC50 ≤1 mg/L, or the LC50 or EC50 ≤100 mg/L. Chronic studies are flagged and given a higher priority in the screening exercise if the maximum acceptable toxicant concentration (MATC) ≤0.1 mg/L, the log K_{ow} ≥5, the chemical is likely to form reactive metabolites, or the chemical is stabile in water and will cause long-term toxicity. These triggers are also used to assist in defining the type of toxicity tests that should be conducted. This toxicity testing scheme is described in more detail in [17,21].

USE OF QSARS IN CHARACTERIZING EXPOSURE

When conducting ranking and prioritization assessments, the exercise must include a component that evaluates potential

exposure of the chemical to receptors of concern. The acute and/or chronic toxicity of a chemical is only part of the picture because a chemical that is more potent than another chemical may have a lower risk when the potential exposure of the chemical to receptors is considered. As described previously, several factors are used in characterizing exposure, including the amount of chemical released to the environment, the persistence within the environment, environmental partitioning, and the chemical's ability to bioaccumulate.

The existence of data gaps within the peer-reviewed literature significantly hampers the evaluation of potential effects and exposure associated with chemical stressors. For instance, the IUCLID system includes empirical data, but in an evaluation of bioaccumulation and biodegradation data for the nearly 2,600 HPVC substances, only 15 and 34%, respectively, had reliable data as defined by EU protocols [15]. Filling these data gaps with empirical testing would be prohibitively expensive. For example, it is estimated that costs for measuring aerobic and anaerobic biodegradation for a single chemical can range from $14,000 to $20,000 (USD) [20].

QSARs for estimating persistence

Environmental persistence refers to the length of time a parent compound, once released into the environment, remains in an environmental compartment (air, soil, sediment, water). Several parameters are used to assess environmental persistence, and many have reliable QSAR models. The EURAM uses aerobic biodegradation to estimate the persistence of a chemical. Only empirical biodegradation data from IUCLID are used by EURAM. Nearly 61% of the chemicals in IUCLID have biodegradation data, and approximately 27% of the chemicals have empirical results for biochemical oxygen demand and chemical oxygen demand studies that can be used to estimate the biodegradability of a compound.

Although EURAM does not use modeled data to estimate persistence, the EU [35] has done extensive research into various biodegradation models for use in conducting risk assessments [38] and recommends the BIOWIN program by SRC [39–41]. The BIOWIN model was developed by evaluating substructures associated with chemicals in a biodegradation database and relating them to qualitative assessments of rate of biodegradability. On the basis of the initial model results [39] and an independent comparison of the BIOWIN multiple linear and nonlinear model results compared to empirical data sets [42], the EU determined that estimated values from BIOWIN for quickly biodegrading compounds are less reliable than estimated values for slowly biodegrading compounds. Therefore, the EU suggests not using estimations of fast biodegradation in environmental risk assessments and using only slow biodegradation results as a confirmation that the substance is not readily biodegradable.

The BIOWIN QSAR programs are used by the ITC in determining aerobic biodegradation. In addition to biodegradation, the ITC uses hydrolysis half-life, atmospheric half-life, and aquatic photolysis half-life as measures of persistence, but reliable QSAR models exist only for estimating atmospheric and hydrolysis half-life [43,44]. The hydrolysis model is appropriate for use only in estimating values for esters, carbamates, halomethanes, alkyl halides, and epoxides. Atmospheric half-life can be estimated for olefins and acetylenic compounds reacting with photochemically generated hydroxyl radicals and via oxidation by ozone.

Environment Canada gathered expert opinion on the use of QSAR models and general rules for estimating persistence in water, air, sediment, and soil [13]. Briefly, the experts suggested approaches to determine the half-life of substances within each environmental compartment. Whether the substance has partitioned into an environmental compartment must be addressed when applying the half-life criterion during categorization. In the absence of other information, the U.S. EPA or EU approaches (see previous discussion) should be used to aid in the extrapolation to half-life criteria for biodegradation. The experts suggested using an hydrolysis half-life model when evaluating persistence in water and, if not available, using either biodegradation, photolysis, or photooxidation models or data. However, it was also pointed out that all these models have limitations and that expert judgment is required when using them.

QSARs for estimating environmental partitioning

Chemicals released into the environment will preferentially partition into specific environmental compartments. The EURAM system uses the Mackay Level I fugacity model to estimate environmental partitioning [45]. In the Mackay Level I model, the compartments used are air, water, soil, bottom sediment, suspended aquatic matter, and biota, with the sizes of the compartments fixed. This model requires input of several physical/chemical properties, including boiling point, vapor pressure, log K_{ow}, and aqueous solubility of the substance. The EURAM system directly inputs empirical or modeled data into the Mackay model. Only the air, water, and soil compartment estimates from the Mackay model are used by EURAM in assessing environmental partitioning.

The ITC uses a variety of parameters to describe environmental partitioning, including the log K_{ow}, soil sorption coefficient, and Henry's law constant. The ITC uses the KowWIN software to estimate log K_{ow}, but other computerized packages exist, including CLOG*P* and SPARC [46–49]. Selecting the proper log K_{ow} value can be critical when conducting risk assessments. For this reason, the U.S. EPA developed methods for selecting the most appropriate measured and estimated log K_{ow} value and, for a limited number of priority pollutants, identified the values selected using these procedures [50]. The sorption coefficient is used to estimate the equilibrium partitioning of freely dissolved chemical to chemical adsorbed to a solid phase, such as soil or sediment. The sorption of a substance can significantly affect its bioavailability. The ITC estimates the soil and sediment sorption coefficients using the PCKoc model [51]. Henry's law constant, which estimates the partitioning between air and water, can be estimated using the HenryWin QSAR program [52].

QSARs for estimation of bioaccumulation

Bioaccumulation is the resulting accumulation and retention of a substance by an organism as a result of uptake from all exposure routes. Bioconcentration is the accumulation of a substance by an aquatic organism as a result of uptake directly from the surrounding water through gill membranes or other external body surfaces. Current QSARs used to estimate the BAF and BCF assume that biotransformation is negligible, that equilibrium has been reached, and that partitioning between the exposure media and lipid phases is the driving force involved in accumulation. Assuming the chemical is sequestered within the lipid components of the organism, log K_{ow} is directly correlated to the estimation of BCF values. Empirical data demonstrate that these relationships are no longer linear

at high log K_{ow} values, with the BCF decreasing when the log K_{ow} is greater than 6. Several theoretical reasons for BCFs decreasing with increasing log K_{ow} include biotransformation of the substances and kinetics related to permeability and solubility of large substances in biolipids [35,53]. Empirical data, from which K_{ow} and BCF relationships are derived, may also be problematic in that assumptions of equilibrium may not have been met in all instances. In addition, the sorption of these substances to organic matter during the aqueous exposure and use of solvents to create supersaturated solutions results in a portion of the chemical not being bioavailable and consequently not accounted for correctly in some measured BCF data.

Because of a lack of available BAF data, the EURAM system uses the BCF to estimate exposure to top predators [8,35]. To account for chemicals that may not partition into biolipids because of size restrictions, substances with molecular weights above 700 are assumed to have a log (BCF) = 0. For all other substances, EURAM uses either measured BCF values that are lipid normalized and, if measured values are not available, uses an adjusted log K_{ow} value to estimate the exposure score for top predators [8].

Under the Degradation Effects Bioconcentration Information Testing Strategies system, the ITC proposes to use BCF values of >1,000 as a means of identifying chemicals of potential concern to the environment. The ITC uses the BCFWIN model for estimating the BCF [53]. Several other reliable models exist, including the model for fish developed by Veith and coworkers and a model for benthic organisms that is used by the EU in conducting more detailed risk assessments [54,55].

Environment Canada is currently assessing recommendations on estimating BAF and BCF values on the basis of input from a panel of experts in the field of QSAR [13]. Although several reliable models exist (see previous discussion), the panel suggested that rules of thumb used by groups such as the ITC (e.g., cross-sectional diameter and molecular weight thresholds) may be useful when evaluating the bioaccumulation of a substance because the bioavailability of the compound may be uncertain.

USE OF QSARS TO CHARACTERIZE EFFECTS IN AQUATIC ORGANISMS

Under the U.S. EPA's ecological risk assessment guidelines, ecotoxicity effects data should support the defined assessment endpoint [1]. Therefore, the toxicity data should describe ecologically relevant endpoints that reflect the sensitivity of the receptor. In screening large inventories, toxicity endpoints are typically related to survival, reproduction, and/or growth. The species that are evaluated are typically those associated with predefined governmental test guidelines or those associated with required data submissions (aquatic organisms).

In an evaluation of new chemicals assessed under the U.S. EPA's PMN program, between 1986 and 1992 approximately 5% of the submissions included ecotoxicity data [5]. In a separate analysis of data submissions for 462 chemicals with ecotoxicity data, less than 3% had chronic test results [56]. The EU's IUCLID system includes significantly more ecotoxicology data. Using data quality criteria defined for EURAM, acute toxicity data for fish and invertebrate species are available for approximately 52 and 43% of the substances, respectively. For chronic exposures, these values are significantly reduced, with approximately 10 and 22% of the chemicals having acceptable toxicity data for fish and invertebrate species, respectively. These data gaps pose problems when evaluating the toxic effects of chemicals to aquatic organisms.

In evaluating toxic effects, calculated endpoints such as LC50, EC50, MATC, NOEC, and lowest-observable-effect concentration (LOEC), obtained from toxicity tests conducted using acceptable standard protocols, are used to compare responses across chemicals. Most regulatory protocols recommend submission of acute lethality data for fish and *Daphnia* and chronic growth and/or reproduction data for algae, fish, and *Daphnia*. Similarly, QSARs to estimate toxicity are generally available for these receptors and endpoints.

A primary uncertainty in applying ecotoxicity QSARs concerns selection of the appropriate model for the chemical of interest. Many QSARs are developed for traditional chemical classification systems (benzenes, phenols, and so on), but within a single chemical class, more than one mode of toxic action may be represented [57]. As a consequence, QSAR development and application have been evolving from a chemical class perspective to one that is more consistent with assumptions regarding modes of toxic action [9,57–60]. Most of these models require some professional judgment and may require input of estimated variables such as log K_{ow}. Therefore, users should ensure that the most appropriate input variables are used.

The ITC uses the Substructure-Based Computerized Chemical Selection Expert System (SuCCSES) to predict toxicity of structurally related chemical classes that have similar modes of action [61]. The SuCCSES uses the models included in the U.S. EPA's Assessment Tools for the Evaluation of Risk (ASTER) system, the U.S. EPA's ECOSAR program, and Optimized Approach Based on Structure Indices Set (OASIS) system to estimate toxic effects to aquatic species [62–65]. The ASTER ranking software selects QSARs on the basis of fragments identified in the chemical structure that have been linked to specific modes of toxic action [57]. These substructure rules were developed using an extensive knowledge base of more than 600 acute toxicity tests, joint toxic action studies, toxicodynamic profiles of physiological responses in fish, and behavioral and dose–response interpretation of 96-h LC50 test results. Using the results from these efforts and principles in the toxicological literature, approximately 600 chemicals were classified into distinct modes of toxic action. Using this knowledge base and information in the peer-reviewed literature, chemical substructure rules were developed for selection of the acute mode of action. The ASTER system limits QSAR models to nonreactive substances, such as those acting through a narcosis mode of action, with all primary models estimating toxicity to the fathead minnow (see Table 2). ASTER includes models for estimating chronic toxicity to fathead minnows on the basis of the acute mode of toxic action (Table 2). The QSARs within ECOSAR were developed on the basis of traditional chemical classification systems. Over 100 QSAR models are included in ECOSAR, representing more than 42 chemical classes. For the most part, the log K_{ow} is required to estimate toxicity, but for some chemical classes, charge density of the molecule may be required as an input variable. The QSAR models were developed using empirical data submitted by industry and data generated by the U.S. EPA's Office of Research and Development [57]. These models have been published elsewhere and are too numerous to describe in this review [63]. The OASIS technology is based on developing databases of molecular descriptors (e.g., steric and electronic indices) and expert systems that use these molecular descriptors to provide on-the-fly predictions of toxicity endpoints.

Table 2. Quantitative structure–activity relationship (QSAR) models for modes of toxic action identified in a database of fathead minnow 96-h LC50 and chronic MATC values. QSARs use the octanol–water partition coefficient (K_{ow}) as the independent variable[a]

Mode of action	QSAR	Source
Acute toxicity (*Pimephales promelas*)		
Nonpolar narcosis	Log LC50 (mol/L) = $-0.94 \log K_{ow} - 1.25$	[104]
Polar narcosis	Log LC50 (mol/L) = $-0.65 \log K_{ow} - 2.29$	[105]
Ester narcosis	Log LC50 (mol/L) = $-0.71 \log K_{ow} - 2.43$	[57]
Uncoupler of oxidative phosphorylation	Log LC50 (mol/L) = $-0.67 \log K_{ow} - 2.95$	[57]
Chronic toxicity (*Pimephales promelas*)		
Nonpolar narcosis	Log MATC (mol/L) = $-0.87 \log K_{ow} - 2.21$	Unpublished
Polar narcosis	Log MATC (mol/L) = $-0.643 \log K_{ow} - 3.43$	Unpublished
Uncouplers of oxidative phosphorylation	Log MATC (mol/L) = $-0.413 \log K_{ow} - 4.63$	Unpublished

[a] LC50 = concentration estimated to cause 50% lethality; MATC = maximum allowable toxicant concentration.

Unlike previous QSAR approaches, the OASIS fuzzy modeling concept assumes that molecules exist as a variety of conformers with solvation and binding interactions capable of compensating for energy differences between conformers during interconversions. Hence, instead of point estimates, ranges of parameter values can be associated with each chemical. The fuzzy modeling concept implemented in correlative QSARs allows for the selection of active conformers, such as when applied to predictions of estrogen receptor binding affinity. The fuzzy modeling concept yielded a new approach for recognition of Common Reactivity Patterns (COREPA) among topologically diverse chemicals eliciting similar biological effects, thus circumventing the problems of conformer alignment and selection [66–70].

Similar to the ASTER system, the EU uses QSARs to estimate toxicity for nonreactive substances. The recommended QSARs are summarized in Table 3 and are based on empirical data sets developed at the University of Utrecht, The Netherlands, and the U.S. EPA [57,60,71–78]. These data sets were reanalyzed for the EU ranking effort [79]. Methods described by Verhaar and coworkers are to be used in determining the mode of toxic action and thereby the selection of the appropriate QSAR model [60].

Environment Canada held a workshop to discuss approaches for defining inherent toxicity and QSAR methods that can be used in estimating inherent toxicity [13]. The workshop resulted in an approach for assessing inherent toxicity. It was recommended that for all discrete organic chemicals, the mode of toxic action should be identified and the list separated by modes of toxic action into reactive substances and nonreactive substances. Empirical data will be used when available, but QSAR models will be required to fill in data gaps. Models exist for the nonreactive modes of toxic action (e.g., narcosis mechanisms), but further research needs to be conducted to better define structure related toxic potencies associated with multiple electrophile/proelectrophile modes of action. Environment Canada is proposing the use of application factors to predict iT to nonhumans for substances having reactive modes of action but no empirical data. The approach by Verhaar et al. [60] would be used to classify chemicals into one of four classes. Application factors would be applied to a nonpolar narcosis model, and the magnitude of the application factor would be based on the selected chemical class.

Many QSAR models currently exist that can predict the effects of a wide range of substances to biota, particularly aquatic biota. The difficulty for regulatory programs is in choosing the appropriate QSAR model or models for application in their new and existing substances programs. In preparation for the QSAR workshop, Environment Canada evaluated model performance of six QSAR modeling packages: ECOSAR, TOPKAT (ver 5.01; Health Designs, Rochester, NY, USA), a Probabilistic Neural Network, a Computational Neural Network, the QSAR components of the ASTER system, and the OASIS system [62,63,67,80–83]. Using a test data set of 130 substances that had not been included in the training data sets of the QSAR models under consideration, Environment Canada compared model predictions for 96-h LC50s to fathead minnows to the corresponding measured toxicity values available in the U.S. EPA's ecotoxicology (ECOTOX) database [84]. The test data set was heavily weighted with neutral organic chemicals of low molecular weight and functionality. Many of the test data set substances also had a nonpolar narcosis mode of action. A variety of statistical measures (e.g., correlation coefficient, slope and intercept from a linear re-

Table 3. Summary of quantitative structure–activity relationships (QSARs) recommended by the European Union for use in estimating toxic effects for substances acting through a nonpolar or polar narcosis mode of toxic action

Species	Endpoint[a]	QSAR[b]	Source
Nonpolar narcosis mode of action			
Pimephales promelas	96-h LC50	Log LC50 (mol/L) = $-0.85 \log K_{ow} - 1.39$	[35]
Brachydanio rerio	28–32-d NOEC, early life stage	Log NOEC (mol/L) = $-0.90 \log K_{ow} - 2.30$	[35]
Daphnia magna	48-h EC50 immobilization	Log EC50 (mol/L) = $-0.95 \log K_{ow} - 1.32$	[35]
D. magna	16-d NOEC, growth, reproduction	Log NOEC (mol/L) = $-1.05 \log K_{ow} - 1.85$	[35]
Selenastrum capricornutum	72–96-h EC50 growth	Log EC50 (mol/L) = $1.00 \log K_{ow} - 1.23$	[79]
Polar narcosis mode of action			
P. promelas	96-h LC50	Log LC50 (mol/L) = $-0.73 \log K_{ow} - 2.16$	[35]
D. magna	48-h EC50 immobilization	Log EC50 (mol/L) = $-0.56 \log K_{ow} - 2.79$	[35]

[a] LC50 = concentration estimated to cause 50% lethality; NOEC = no-observable-effect concentration; EC50 = estimated concentration where 50% of the organisms display adverse effects.
[b] Log K_{ow} = log of the octanol–water partition coefficient.

gression analysis, mean absolute and squared difference between log prediction and log measured toxicity, percentage of predictions within factors of 2, 5, 10, 100, and 1,000 of measured toxicity values) indicated that the Probabilistic Neural Network model had the best model performance for the full test data set of 130 substances. The rank order of the remainder of the models depended on the statistical measure employed. The TOPKAT modeling package also had excellent model performance for substances within its optimum prediction space. Only 37% of the substances in the test data set, however, fell within this optimum prediction space. For a more complete overview of the approaches undertaken in this analysis, see the paper by Moore et al. in this review issue.

RELATING EFFECTS TO EXPOSURE

It is important to relate the effects associated with a chemical stressor to known or estimated exposure concentrations. In risk assessments such as those done for the U.S. EPA's ITC, Environment Canada, and EU, estimates of environmental exposure are made using fate and transport models. The EURAM model predicts the amount of substances that could be emitted and available to exposure using predefined general use categories. The general use categories include closed systems (substance remains within reactor/closed vessels), uses into or onto a matrix (substance is incorporated into products, and the substance would not be released into the environment), nondispersive uses (exposure limited to workers with knowledge of processes), and wide dispersive uses (uncontrolled exposure). For each of these general use categories, the amount of substance identified as imported or released into the environment is obtained from IUCLID and used in EURAM to estimate the total emissions of a substance. The emission score is incorporated into EURAM's final environmental exposure score [8].

The ITC uses the same methods for estimating exposure assessment as employed under the PMN review process [36]. Potential environmental releases to the water compartment are estimated using either a percentile stream flow model or a probabilistic dilution model [36]. The probabilistic dilution model, unlike simple dilution calculations, attempts to account for the natural variability of stream flows and effluent flows when comparing concentration values to concern levels. To account for the variability, a probability distribution of stream flows is incorporated into the simple dilution calculation. It is this difference that permits the risk assessor to estimate the days a chemical exceeds a concentration of concern (for the protection of aquatic life).

Environment Canada is currently developing guidance on the methods and approaches used to conduct screening-level risk assessments. Most of the environmental exposure predictions will be carried out using models similar to those used by the EU and the U.S. EPA.

IMPACTS OF PESTICIDES IN AN IOWA (USA) WATERSHED

An example of a screening and prioritization exercise is the evaluation of a set of pesticides and herbicides identified in a midwestern watershed for the U.S. EPA and U.S. Department of Agriculture's Midwest Agrichemical Surface/Subsurface Transport and Effects Research (MASTER) program. For this effort, the U.S. EPA's ASTER ranking software was used [62]. Similar to EURAM, the ASTER ranking software combines into one system many of the same models used by the U.S. EPA's ITC and the EU and proposed for use by Environment Canada [57,62]. This system was developed and has been used in the screening of large data sets within the U.S. EPA. The ASTER system links the aquatic toxic effects data component of the U.S. EPA's ECOTOX database and the physical/chemical properties database of QSAR [84]. In the MASTER evaluation, ASTER was also linked to the terrestrial toxic effects component of the ECOTOX database. The goal of the MASTER program was to develop ecologically sound and economically feasible agricultural management practices. A component of this research effort was to develop a computer-based risk assessment system utilizing screening-level effects and exposure assessment data for agrichemicals and to rank the potential for adverse impacts among insecticides and herbicides registered for corn and soybeans. Under this effort, 49 registered agrichemicals historically used in the Walnut Creek watershed near Ames, Iowa, were selected for analysis (for details, see [85]).

The ASTER ranking software scores each chemical on the basis of acute or chronic toxicity to aquatic organisms (plants, invertebrates, and vertebrates) and birds, bioconcentration in fish, environmental partitioning based on the Mackay Level I fugacity model, and environmental persistence based on biodegradation half-life [85]. The ASTER system was the primary shell used to access empirical data (e.g., ECOTOX), QSAR models, and expert systems. Predictive models were used to estimate ecotoxicity endpoints, chemical properties, biodegradation, and environmental partitioning when empirical data were unavailable. Acute toxicity QSARs are based on the predicted mode of toxic action of the compound [57]. Within each species group, the most potent toxicity endpoints were selected for the final ranking. The LC50, EC50, LOEC, and MATC values for lethality, immobilization, growth, and reproduction were preferentially selected. Only oral dosing studies using median lethal dose (LD50) were used to assess the avian species score. Only the water and sediment compartment estimates from the Mackay model are used by the ASTER ranking system in assessing environmental partitioning [45]. The model for fish developed by Veith and coworkers was used to estimate the BCF [54]. The ASTER ranking system incorporates a multivariate biodegradation model that uses eight principal components to explain variations in biodegradation [86]. Using the results of this principal component analysis, relationships between chemical substructures and biodegradation half-life rates were identified and developed into an expert system. Threshold values for each ranking parameter are defined in Table 4. Because this project focused on agrichemicals used in the Walnut Creek watershed, only data for freshwater test organisms were examined. Species indigenous to the Walnut Creek watershed or the central United States were selected over nonnative species.

The ASTER ranking system does not include a means of estimating environmental emissions. Therefore, in addition to providing rankings, a final component of the risk screening of agrichemicals was a comparison of toxic effects data for mallards, freshwater fish, and aquatic invertebrates to reported surface water concentrations of agrichemicals as an aid in formulating more detailed risk assessment problems (Fig. 1). This comparison of stressor levels in surface water and known or estimated ecological effects under laboratory conditions assists risk assessors in making decisions on the potential hazard associated with a chemical release into the environment.

Table 4. Parameter scoring used in the ASTER (Assessment Tools for the Evaluation of Risk) ranking system [85]

Score	Acute toxicity[a] (μg/L)	Chronic toxicity[a] (μg/L)	Acute avian toxicity (mg/kg)	BCF[b]	Environmental persistence (d)	Environmental partitioning[c] (%)
5	<1	<0.1	<1	≥5,000	≥15	≥80–100
4	≥1–50	≥0.1–5	≥1–50	≥1,000–5,000	—	≥60–80
3	≥50–500	≥5–50	≥50–500	≥500–1,000	4–15	≥40–60
2	≥500–1,000	≥50–100	≥500–1,000	≥100–500	—	≥20–40
1	≥1,000	≥100	≥1,000	<100	<4	<20
0	No empirical data or estimated value available					

[a] Used for ranking aquatic vascular/nonvascular plants, aquatic invertebrates, and aquatic vertebrate species groups.
[b] BCF = bioconcentration factor.
[c] Sum of environmental partitioning estimates for water and sediments using MacKay Level I fugacity model [45].

DISCUSSION

The chemical ranking and prioritization techniques presented in this paper illustrate the means whereby screening-level risk assessments can be facilitated. In addition, these techniques and associated knowledge bases can be used to efficiently establish a conceptual model within the problem formulation stage of an ecological risk assessment. This paper focused on screening of large data sets by various governmental entities and the application of a screening tool for assessing agrichemicals identified in an Iowa watershed, but other applications of these types of screening methods exist [10,87–97]. The use of QSARs for screening-level risk assessments is limited typically to chemicals that act through nonreactive modes of toxic action. The development of screening tools for use in ranking and prioritizing chemicals that act through more specific mechanisms is an area of active research. For example, the U.S. EPA has been developing tools that look at common reactivity patterns for multiple chemical conformers to predict estrogen receptor binding affinity to rank and prioritize chemical for further endocrine disruptor tiered testing [66–70]. The development of the COREPA and related approaches are summarized by Schmieder et al. in this review series.

Further advancement of QSARs for ranking and prioritizing chemicals of concern will benefit from the development of consistent knowledge bases of high-quality physical/chemical properties and toxic effects data for use in screening priority pollutants. In addition, existing knowledge bases must be evaluated as to the reliability of the data for use in conducting risk assessments or developing QSARs. Both the ASTER ranking system and the EURAM model use toxicological rules, or filters, to identify the best data for use in a screening exercise or QSAR development. However, these filters are not a rigorous evaluation of the primary data. These filters are related generally to standard bioassay protocols reported in a study (e.g., was the chemical concentration measured?) but do not evaluate the correctness of the methods used in deriving the empirical data point (e.g., was the analytical method appropriate, and were quality assurance measures met, such as percentage spike recovery?).

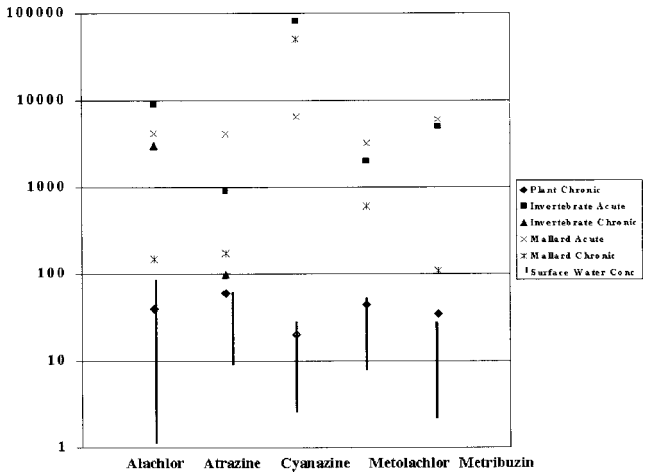

Fig. 1. Adapted from Russom et al. [85]. Comparison of surface water concentrations and toxic effect results for selected agrichemicals.

All the assessment tools discussed in this paper rely on QSARs derived from studies with aquatic organisms. Because aqueous toxicant exposures to fish and invertebrates result in direct uptake across respiratory surfaces into the blood, organisms readily achieve steady state and thereby facilitate a relatively straightforward means to relate external (aqueous) chemical concentrations to in vivo toxicological responses. While a similar logic holds for QSARs based on respiratory exposures to mammals (e.g., relationship between toxicant air concentrations and biological or toxicological activity), these data are limited [98–103]. Because the majority of toxicity data for mammals, birds, and terrestrial insects is based on single or multiple oral and dermal exposures, the toxicokinetics associated with estimating internal (e.g., blood) concentrations can be difficult, and the development of QSARs from such toxicity data can be problematic unless an internal steady-state concentration of the chemical can be estimated. The use of QSAR models to predict the absolute toxicity (e.g., LD50 values) of chemicals to terrestrial organisms following oral or dermal exposures is not possible because under these scenarios the concentration of the substance in the animal's blood is not at steady state with the chemical's concentration in the exposure medium. Nevertheless, it is reasonable to assume that mode-of-toxic-action expert systems derived from studies of aquatic organisms could be used to classify intrinsic toxic potential of xenobiotics across organisms. Thus, to the extent that basic molecular, biochemical, physiological, and morphological processes are conserved across species, SARs for identifying intrinsic toxic potential and ranking relative inherent potency to initiate toxicological events may be readily extrapolated.

It must be stressed that these prioritization and ranking protocols attempt to provide a conservative screening of the potential effects associated with exposure to a chemical stressor; however, several significant issues are not addressed with the QSARs used. For instance, these methods focus on discrete

organic chemicals, so additive, synergistic, or antagonistic effects of chemical mixtures are not addressed. However, mode-of-action-based QSARs do facilitate the identification of compounds likely to act via the same mode of action, and for these compounds it can be assumed that a concentration–addition response will be exhibited, assuming linearity in the dose–response curves. These methods also do not account for potential bioactivation and the resulting toxicity of metabolites. For example, this is especially important when assessing risk associated with chronic exposures to proelectrophiles or prohormone receptor ligands. Finally, the lack of reliable models of metal complexes limits the usefulness of these screening tools.

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