Introduction and aims

In silico technologies encompass a large number of approaches that may assist in the prediction of toxicity and fate of new and existing chemicals. The aims of this paper are to introduce briefly the concept of in silico techniques for toxicity prediction, evaluate how and where they may be used for regulatory purposes, their implementation and acceptance criteria, and finally point out key areas for further research. This paper has been written with particular emphasis on regulatory usage of these approaches. It should also be noted that many of the techniques described below have considerable potential use in product development. Finally, whilst every effort will be made to keep this article up-to-date, in such a fast moving area, there will inevitably be some redundancy of the information even with expeditious publication.

In silico technologies

There has been an appreciation that biological activity is related to chemical structure since the mid-nineteenth century, and, from the end of that century, that toxic potency may be related to physico-chemical properties (Schultz et al., 2003). The last century has seen a maturing of this science into what are now frequently termed “in silico” methods for the prediction of toxicity and fate. As a term of reference for this paper, in silico is taken to imply a broad group of techniques including the use of existing data, read-across (also known as analogue or category approaches), quantitative structure-activity relationships ((Q)SARs) and expert systems. The reader should be aware that others may not use such expansive terminology and may take in silico to cover fewer of these topics. In silico approaches are of interest as they allow predictions of toxicity and fate from chemical structure alone, thus supporting the reduction in animal testing. For a full overview of the development and use of in silico methods the reader is referred to Cronin and Livingstone (2004).

Should (acceptable) data for a particular chemical for an endpoint of interest already exist, there should be no need to predict or measure toxicity. There are many sources of toxicity and fate data for use, the most accessible of which have been reviewed recently by Cronin (2005). There are many places in the literature and on the internet containing toxicological information, one of the best starting places being the TOXNET online...
database [http://toxnet.nlm.nih.gov/] (Cronin, 2005). There are also several commercial databases of toxicological information of varying cost and quality. Regulatory data could provide a very amenable source of information for risk assessment, although many of these databases are not generally openly available. Associated to the regulatory data are those being generated for the assessment of the High Production Volume (HPV) chemicals. Other sources of data are, of course, in-house repositories, although again these will not be freely available for the foreseeable future. As well as providing a resource for regulatory assessment, existing data may also be suitable to assist in model development and evaluation.

Whilst there are many existing data available, there are also a number of concerns about their use. The most fundamental concerns address the quality and relevance of the data, and whether they are even relevant for the decision being made, i.e. are they acquired according to an acceptable or reliable protocol, etc. Other issues relate to the practicalities of retrieving existing data, especially from historical databases, that may be paper-based, or stored on incompatible electronic databases. Efforts to record toxicity data onto freely available and widely compatible formats with mark-up languages (such as xml) should be encouraged. Furthermore there is the ever-present problem of the release, or use of, commercially sensitive data. As noted above, the current dogma is that many such data will not be released voluntarily, and due to the cost and effort involved in organising such data, it may not be possible to do so practically. There is also the complex problem of who will host, maintain and update databases of toxicological information. Despite these problems, there are two illustrations of what may be done. The Distributed Structure-Searchable Toxicity (DSSTox) Database Network has been developed as a project of the US Environmental Protection Agency’s (EPA) Computational Toxicology Program [http://www.epa.gov/nheerl/dsstox/]. The VITIC toxicological database is being developed by Lhasa Ltd. [http://www.lhasalimited.org/].

Read-across, category and analogue approaches are based on the assumption that “similar” compounds will have “similar” properties. Thus, if a compound is “similar” to a known toxic compound, the probability of it being toxic will be high. In some ways this can be considered to be a simplification of the traditional use of structure-activity relationships (SARs), although the mechanistic nature of the SAR need not be defined formally in read-across. There is effort to develop at least one tool (the US EPA’s Analog Identification Method) to search databases and perform read-across automatically. It should be noted that this tool is not publicly available at the time of preparation of the manuscript, but is undergoing beta-testing.

(Q)SARs attempt to relate the toxicity of a series of chemicals to their physico-chemical and structural properties. In theory, models of some form can be developed for most toxic endpoints (i.e. qualitative or quantitative) using any of a wide variety of molecular descriptors and statistical techniques (Cronin, 2004a). (Q)SARs offer the capability to make a prediction from chemical structure alone and have the advantage that they may shed some light on the mechanism of toxic action. Models may be standalone, e.g. some form of regression equation, or be automated into a formal expert system. Expert systems may be defined as being “any formalised system, not necessarily computer-based, which enables a user to obtain rational predictions about the toxicity of chemicals” (Dearden et al., 1997). There are many approaches and philosophies to develop expert systems, and they have been applied to predict toxicity and fate by regulatory agencies worldwide (see the next section). There are a large number of expert systems available, both as freely available software and commercial systems; these are well reviewed by a number of authors including Combes and Rodford (2004).

Regulatory applications of in silico technologies

There is considerable use of (Q)SARs and other in silico methods to predict toxicity and fate by Regulatory Agencies worldwide. The area in which (Q)SAR has been used by regulatory agencies is very well covered and reviewed (Cronin et al., 2003a, 2003b, 2004b). It is generally accepted that in silico methods will be used for:

- prioritisation of existing chemicals for further testing or assessment
- classification and labelling of new chemicals
- risk assessment of new and existing chemicals

Very briefly, in silico technologies have been used by Health Canada in relation to the Domestic Substances List; by the Danish Environmental Protection Agency to develop a (Q)SAR database and support system; by the Japanese National Institute of Technology and Evaluation (NITE) to examine targets under the current Chemical Substances Control Law (CSCL); extensively in the United States by the Environmental Protection Agency (e.g. EPISuite, OncoLogic, ChemSTEER, E-FAST, PBT Profiler, Analog Identification Method) and by the Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER).

In the European Union the current focus of much effort in in silico toxicology is towards the ultimate implementation of the Cosmetics Directive and the Registration, Evaluation and Authorisation of Chemicals (REACH) legislation. Whilst there is much international effort to use (Q)SARs to predict toxicity and fate, the emphasis of the remainder of this manuscript will be on the use of in silico methods for the forthcoming REACH legislation.

Implementation of in silico technologies

There appear to be clear benefits of the use of in silico tools to make predictions within the framework of the REACH legislation. In particular, in silico methods play a clear role in Integrated Testing Strategies for toxicological endpoints (Combes et al., 2003; Worth and Balls, 2002). Existing data, as well as predictions from read-across and (Q)SARs, are well established as part of the strategy. Whilst much work has been done and is, of course, on-going, integrated strategies are still required for some toxicological endpoints. In addition, more consideration will be required as to the validation of these strate-
The implementation of in silico methods (particularly in REACH) will be linked strongly to issues of the acceptance of the methods and the evaluation of methods and any predictions from them. At the time of preparation of this paper, there are a number of international implementation activities on-going and planned. These include the various REACH Implementation Projects (RIPs) and RIP 3.3 in particular. There are also a number of industry-sponsored initiatives (e.g. CEFIC-LRI projects) as well as (non-industry) projects being organised through the European Chemicals Bureau at Ispra, Italy. A number of projects are being funded by European Union Framework and Non-Framework programmes as well as a number of national governmental initiatives in member states. No specific details of these projects are provided as many are on-going or are due to commence shortly. The interested reader should contact the relevant funding bodies for more details.

Acceptance

The acceptance of predictions from in silico toxicological methods is a complex matter. There is a clear role for the characterisation and evaluation and possible validation of in silico models. With regard to this issue, Annex IX of the REACH Proposal states:

“results obtained from valid (Q)SARs may indicate the presence or absence of a certain dangerous property. Results of (Q)SARs may be used instead of testing when the following conditions are met:

- results are derived from a (Q)SAR model whose scientific validity has been established
- results are adequate for the purpose of classification and labelling and risk assessment
- adequate and reliable documentation of the method is provided”


The quest for methods to assess “scientific validity” has resulted in a number of activities to assist in the development of a scheme to “validate” (Q)SARs. At this point it should be noted that the (Q)SAR community has historically used the term “validation” in a somewhat different sense, to indicate the statistical quality and robustness of a model. This has, at times, caused confusion in the (Q)SAR community with the broader meaning of “validation” in the regulatory sense.

A set of criteria for the validation of (Q)SARs has been agreed upon by the Organisation for Economic Co-operation and Development (OECD), the so-called “OECD Principles”. These state that a (Q)SAR should be associated with the following information:

- a defined endpoint
- an unambiguous algorithm
- a defined applicability domain
- appropriate measures of goodness-of-fit, robustness and predictivity
- a mechanistic interpretation, if possible.

The results of a pilot study to evaluate these criteria are available at: http://www.oecd.org/document/23/0,2340,en_2649_34365_33957015_1_1_1_1_00.html and, at the time of preparation of the manuscript, four “validation” studies are on-going, co-ordinated by the European Chemicals Bureau.

When one begins to attempt to validate a (Q)SAR, it soon becomes apparent that a considerable number of challenges must be faced. For instance, there is sparse availability of toxicity data for test sets to allow for a true assessment of predictivity. There are also considerations for commercial models that may not wish to have their models made transparent. It is also important that any validation process is not seen as a competition. There should be no winners in this activity, merely an appreciation of the merits (or otherwise) of individual predictions.

The validation process has therefore become somewhat controversial, with some calls for complete validation (Balls and Combes, 2005). To broaden the debate, it should be remembered that in terms of Annex IX quoted above, “valid” means valid for a specific purpose. It can be construed that the amount of information necessary to demonstrate validity should be context-dependent. This can be considered in relation to the acceptability of making a wrong decision and the acceptability of not being able to make a decision at all, due to lack of experimental data. Validation exercises (such as those being undertaken at the time of preparation of this paper) may be better served if they focus on characterising (Q)SARs according to the OECD principles as opposed to considering a model as being “validated” or “non-validated”. In other words, if no experimental data are available, a prediction may have some value, providing the limitations of the model and the prediction are appreciated and understood. Thus, for instance, it may be appropriate to consider some level of confidence in a prediction of activity within the framework of the OECD principles.

Guidance Document(s) are required in order to facilitate the use and validation of (Q)SARs. OECD Guidance Documents on (Q)SAR Validation and Case Studies on regulatory acceptance of (Q)SARs are being planned and executed. Other activities include the development of a (Q)SAR Application Toolbox to assist the user in the application of in silico techniques. These and other requirements are discussed below.

Future directions and needs

Whilst a number of in silico tools are already available for use and are being used for regulatory purposes, there is still a requirement for on-going development of models, tools and guidance. Some of this development is planned and ongoing and much is funded at an international level (see, for instance the implementation section). With so much effort being placed in the development of in silico tools, there is a clear need for coordination of these efforts. Much is currently being performed and further leadership and planning will be required and is underway. There are specific issues to be considered, for instance, the availability of toxicity and fate data for modelling and model evaluation. There is recognition of the need for more data, but few definitive ideas of where these data will be sourced,
how to assess their consistency and reliability, how to perform quality assessment and assurance, storage and handling, and how to deal with commercially sensitive data. Other issues with regard to the application of \textit{in silico} tools relate to the degree of validation that may be required for a model for any particular purpose; the formal definition and consideration of the applicability domain of a model; and how different predictive approaches may be considered in terms of consensus modelling. Education of model users (i.e. from regulatory agencies) and appropriate guidance documents (as described above) is also an area that will need much effort, and probably much good will from the trainers. There are, of course, many other equally pressing needs for the development of good \textit{in silico} tools for the prediction of toxicity and fate. Few, if any, are insurmountable, and it is positive to see that much is currently being planned, performed and achieved at the international level to resolve all these issues.

**Conclusions**

\textit{In silico} technologies cover a wide variety of approaches to predict toxicity and fate. Many of these are relevant to regulatory agencies. The REACH legislation has focussed the thoughts and efforts of the scientific community to address and resolve the issues faced by this “incomplete” area of science. Implementation of these approaches, in terms of providing user-friendly tools, education and acceptance criteria, is still required at many levels. Ultimately, modellers (developers and users) must accept that the use of predicted values is not an easy, quick and simple option, and pragmatism will be required.

**References**


**Acknowledgments**

Far from being my own ideas, the thoughts presented in this paper are the culmination of hours of discussion over many years with a multitude of excellent scientists across the world. I’m certain we don’t agree all the time, but I do thank them all for the intellectual stimulation they have provided.

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Roles for QSAR in Risk Assessment

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Summary
Early pioneers in quantitative structure-activity relationship (QSAR) development believed in the premise that laboratory experiments should not be performed without a firm expectation of the results before going into the laboratory. The value of QSARs in risk assessment will be to provide us with those expectations for a wide variety of exposure and hazard assessment endpoints before the decision to require specific testing is made. Most of the current QSAR models are limited only by the lack of designed databases; however, as they evolve, QSAR models for most endpoints will undoubtedly be used to provide us with test expectations for thousands of untested chemicals. In so doing, QSAR will complement the 3Rs with a powerful new tool to minimise animal testing that is not likely to influence regulatory decisions. If it is true that 95% industrial chemicals have a lower probability to be classified as an endocrine disrupting chemical (EDC) than n-butyl aniline, avoiding testing on those chemicals can be achieved by QSAR screening. With the recent development of computer simulators of metabolic activation (e.g. the virtual liver), improved QSAR models for skin sensitisation, respiratory irritation and genotoxicity will follow quickly. Finally, the integration of QSAR models with in vitro methods holds great promise for the prudent use and interpretation of our testing and assessment resources.

Keywords: QSAR, in silico, REACH, non-animal, model domain

Introduction
Studies of quantitative structure-activity relationships (QSAR) can be traced back in the literature for more than a century. Whenever QSAR has been applied to the more complex problems in medicinal chemistry and toxicology, the models have had to be greatly simplified in order to fit the computational capabilities of the times. The publication of simplified models has often led to misapplication of the model as well as fuelling criticism of QSAR.

This millennium has ushered in vast new computational capabilities for QSAR. Just as has happened with other areas of science incorporating modern computing, it is tempting to describe QSAR in new terms such as “in silico”, which make it appear to be a new specialised field or technology. It is important for us to remember, however, that QSAR is not a discipline or a field of research. Rather, it remains a scientific approach that can be applied to many scientific fields to understand the determinants of forecasting results of experimental methods involving chemicals before the experiments are performed. Together with international concurrence on the principles for validation of QSAR models, the next decade promises to bring unparalleled application of QSAR in risk assessment.

The evolution of the Registration, Evaluation and Assessment of CHEmicals (REACH) legislation in Europe may offer in silico methods a central role in fulfilling data requirements over the next decade. The principles of validation of QSAR were articulated in the Setubal Principles (Jaworska et al., 2003), which have, after slight change in emphasis, become OECD principles for the validation of QSAR. One of the themes in the principles of validation for QSAR models is transparency. It is generally understood that, for QSAR models to be accepted by the regulatory community, transparency in terms of availability of the data and of the algorithm for the model is sought. This level of transparency is largely one of documentation, sufficient to allow the model to be reproduced by others, a basic tenet of science in general. Perhaps less frequently emphasised is the transparency of the mechanisms that underpin the model. Transparency in this mechanistic context is the extent to which the model can explain why the estimated endpoint value was estimated as it was and how a change in structure might affect the results.

Before describing some of the important roles for QSAR in regulatory risk assessment, it is important to review the basic elements of the QSAR approach. The first element of QSAR is to select a well-defined endpoint of chemical or biological activity to be modelled and to compile a database for chemicals that have been tested. The second element of QSAR is to compile a list of molecular descriptors for the structure of the chemical in the database. The third element of QSAR is to apply statistical methods to explore the variances in the data and identify useful relationships between the molecular descriptors and the endpoint of activity. The forth element of QSAR is to formulate a hypothesis about the observed relationship and modify the database in a way that will test the hypothesis. Many transparent QSAR models include the first three elements of the QSAR approach, but the majority of QSAR models offer scant records of efforts to redesign the database to reveal underlying mechanisms.

The lack of transparency regarding structural requirements for applying a QSAR leads to what I will call the “domain conundrum”. Without a mechanistic basis for a model, it is difficult to
select chemicals that can really validate the model or explain the reasons the model can be used for a specific chemical in a regulatory application. To escape this conundrum in validation, the QSAR model domain is often defined as a multidimensional parameter space derived from the molecular descriptors in the training set. Defining a domain in these terms is an implicit argument that all chemicals that fall within that structure space should be expected to conform to the model, which is seldom correct and can easily be shown to be invalid.

**QSAR in a nutshell**

The essence of QSAR is the fundamental belief in chemistry that expects similar chemicals to behave similarly. As such, the essential role for QSAR is to serve as a guide in the selection of chemicals for testing of mechanistic understanding and not the after-the-fact modelling of data on a small number of chemicals. Like any model, QSAR can improve our hypotheses about why some chemicals are active and some are not active, or at least make the formulation of hypotheses more efficient. Formulating hypotheses and then selecting new chemicals for testing is the scientific method, and the only way to create a robust model with clear boundary conditions.

The basic steps in building a QSAR model for an iterative process begin with the compilation of a database for the endpoint for which the model is intended. Molecular descriptors are calculated for each chemical represented in the database and exploratory statistical methods are used to identify potential relationships. From the analysis of outliers, hypotheses are generated to examine those relationships by adding new chemicals to or subdividing the database. The revised training set is again analysed statistically and the process repeated. The hypotheses generated in the refinement of the model form the basis for defining the model domain in mechanistic terms. If one takes a dataset of biological effects, calculates 300 parameters for each of the chemicals and develops a statistical relationship, the resulting “model” represents only a part of one QSAR development step. The domains of such models must be described only as boundaries in a parameter space for the molecular descriptors that were statistically important in the model.

**Roles for QSAR in regulatory applications**

The goal of QSAR is not to produce a series of models to be used in place of laboratory tests, but rather to improve both the design and strategic use of test methods. QSAR is a perspective with which one can approach complex problems with techniques to distinguish important problems. QSAR improves hypothesis generation in research involving chemicals and, in so doing, tends to improve the experimental design in many area of scientific specialisation.

The short-term role for QSAR in regulatory risk assessment will be to add clarity to existing processes and make them more efficient. In OECD countries, the emphasis for QSAR will be to assist in the development of chemical categories based on common chemical behaviour. When categories are formed as analogues, the opportunity exists to extend the test data for any members of the categories to all members of the categories through methods of read-across. In developing categories both in classification and risk assessments, information is needed regarding the metabolites of the chemicals. Empirical data for metabolism is sparse and piecemeal, and QSAR-based metabolic simulators can provide information to strengthen these processes. Also in the short-term, there are sufficient QSAR models mature enough to use them to begin establishing testing and assessment priorities.

In the longer-term, which will allow time to improve QSAR models for important endpoints, the highest priority will likely be the use of QSAR to estimate missing values for screening information data set (SID) endpoints. In addition, a number of studies are demonstrating that QSAR models can be integrated with bioinformatics and high throughput testing to improve the efficiency of these capabilities. Combining all these uses of QSAR, the most significant role for QSAR will be to create a hypothesis-driven sequential testing strategy, which will eliminate all of the battery testing in risk assessment that is not ultimately used in the risk assessment (Bradbury et al., 2004). Whether these approaches are called intelligent testing strategies or 3rd generation risk assessment paradigms for chemicals, QSAR models will be central to making the logical decisions for testing requirements.

**Historical barriers to QSAR**

In addition to the point made earlier that predicting many forms of chemical activity was a larger computational problem than could be realistically approached with computers in the past, there are three barriers to QSAR modelling which have limited its development. The first of these has been chemical speciation and conformational analysis. Most QSAR models use molecular descriptors computed for parent chemicals even though different species are known to exist in natural systems. As stereoelectronic descriptors come into use, the gas phase minimum energy conformation of the chemical is commonly used, even though many conformations for flexible molecules would be expected at ambient conditions. As the sensitivity of QSAR models to conformational assumptions becomes more apparent, the importance in understanding the influence of conformation will grow. Fortunately, methods are now available to remove the historical conformational barrier.

The second historical barrier to QSAR modelling arose from the fact that the parent chemical structure is often not the actual toxicant causing the effect. Like many in vitro tests methods, QSAR models could not account for metabolic activation of chemicals. Mixing chemicals that were directly active with those that must be changed to toxic metabolites in a common training set usually creates outliers in modelling. Within the past five years, the first generation of metabolic simulators, which can convert parent chemicals to a plausible family of metabolites, have been developed. These computerised simulators of metabolic processes are limited only by the amount of high qual-
ity, systematic data on metabolism and are likely to be refined greatly over the next five years.

Since running a QSAR model both on a parent chemical and its 30-50 plausible metabolites can usually be accomplished “on the fly”, what was a historical barrier will soon be a routine check for possible metabolic activation for specific models.

The third historical barrier to QSAR modelling has been the modelling of chemical reactivity and reactive toxicity. Chemical reactivity is important to model because it represents a series of mechanisms by which chemicals bind to cellular targets and cause toxic effects at low concentrations. Chemical reactivity is difficult to predict because the reactivity is due, in part, to inducible properties of chemicals as well as the more static properties of chemicals. The stereo electronic structure of an isolated chemical can change significantly when it is in water or near membranes, proteins and DNA. Developing a formalism for modelling the inducible properties of chemicals to estimate what molecular interactions are most probable remains a challenge for QSAR modellers. Because reactive toxicity includes so many important biological effects for risk assessment and spans both genotoxic and non-genotoxic effects, it is a major gap in the ability of QSAR to respond to the need of risk assessment.

**Framework for reactive toxicity models**

Reactions of electrophiles with these nucleophiles give rise to one important distinction between reactive toxicity and non-reactive toxicity. Reactive toxicity encompasses the biological effects and measurable adverse outcomes resulting from an irreversible reaction of a xenobiotic chemical with endogenous molecules including proteins, nucleic acids, and lipids. While reactive toxicity includes protein and/or lipid oxidation, conjugation reactions, and the broad spectrum of covalent reactions, we have narrowed the breadth of possible reactions to begin illustrating use of the reactive toxicity framework to two-electron covalent reactions.

Molecular interactions between foreign chemicals and cellular components can initiate or disrupt cellular/organism processes and lead to a wide array of adverse outcomes, including acute failure of energy flow and nerve function, skin irritation/sensitisation, immune system dysfunction, reproductive and development impairment, idiosyncratic organ failure and death, mutagenicity and carcinogenicity. Clearly, since chemicals from different classes can cause similar biological effects, a single chemical can cause multiple biological effects, and many chemicals are “activated” by metabolic processes so the parent chemical is only a “carrier” and not the ultimate toxicant, a conceptual framework that clarifies the many controlling factors is needed.

All of these controlling factors, whether they be biochemical, cellular, organ or systems-based, converge at the point where a molecular initiating event occurs. Consequently, the reactants as well as the reactions involved in those molecular initiating events form the centrepiece of the conceptual framework presented in this work. In figure 1, all of the chemical and biochemical reactions preceding the molecular initiating event (upstream events) require chemical speciation models and metabolic simulators to forecast the relative probabilities of occurrence for important chemical species. Predicting the possible interactions leading up to the molecular initiating events is the role of QSAR modelling.

The sequence of biological effects leading from the molecular initiating events to a specific adverse outcome (downstream events) is a separate portion of the overall toxicity pathway and requires biological models to predict the ultimate consequence of the molecular initiating event. These biological models may often be the same models used in many *in vitro/in vivo* endpoint extrapolations; however, the proposed framework offers an important advantage for the development of endpoint extrapolation models. *In vitro/in vivo* extrapolations may have a model application domain that is not readily apparent from empirical test data alone. Mixing chemicals from different domains in an *in vitro/in vivo* endpoint extrapolation model can cause the same prediction errors as would be found if QSAR models were used outside the model domain. In the proposed conceptual framework, information from the domain of application for a chemical can be used to confine endpoint extrapolation models to more mechanistic domains and make them more reliable.

As a central organising principle, therefore, the International QSAR Foundation is identifying important molecular initiating events involving binding of chemicals with important cellular targets. From that starting point, each specific initiating event is used to group chemicals based on the mechanistic ability of the chemical to cause the molecular initiating event to occur. From those same molecular initiating events, the biological effects that result from the disturbance are grouped by the level of biological organisation represented by the effect endpoints as well as the route of exposure and dose regime. Since a given reactive toxicant may interact with numerous cellular targets, thereby causing numerous biological effects, the potential of a chemical to cause a specific biological effect must be estimated by understanding the relative reactivity, or selectivity, of the chemical toward an array of cellular targets. A systematic description of the selectivity of reactive chemicals for cellular targets is the reactivity profile of chemicals (Shultz et al., 2005).

This framework improves the endpoints that are to be modelled by QSAR by removing all of the variability introduced by the biological testing. In short, it increases the separation of the relative problems of predicting chemical reactions with QSAR models and the biological consequences with biological models. The approach is to begin generating systematic databases for electrophile/nucleophile reactivity across the spectrum of soft to hard electrophile/nucleophiles. These data are used, in turn, as independent variables to explore for correlations with downstream effects. When potential models are found, the training sets are redesigned to test the causal relationships.
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