

White Paper on the (Q)SAR Initiative in India for Global Regulatory Programs

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Study conducted by the Task Force for “IT Based Services Under REACH”

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Introduction

This White paper looks at the need and opportunity to use Quantitative Structure Activity Relationships or (Q)SAR to estimate the value of unknown physical, chemical, biological and environmental properties of chemicals based on known or computationally accessible properties, as may be relevant to Global Environmental Regulatory Programs such as the REACH program of the European Union.(1). In general it intends to leverage Indian strengths in IT, basic sciences and technology, to exploit the opportunity and need that has arisen through such Global Regulatory Programs, through the creation of a framework and development plan, as indicated in this white paper.

About the REACH program

A Draft Chemicals Regulation was launched by the European Commission in October 2003 called REACH. It proposes the establishment of a sustainable chemicals policy. The REACH Program of the European Union is expected to have entry-into-force (eif) by 2006 (2). REACH envisages an extensive system of assessing the physico-chemical, toxicological and environmental properties of chemicals based on their tonnage and perceived impact. (1)

REACH codes for the **R**egistration, **E**valuation, **A**utorization of **C**hemicals in the European Union.

Registration requires industry to obtain relevant information on their substances and to use this information to manage them safely. All chemicals manufactured or imported into the European Union above 1MT will be required to undertake a registration process initiated by the manufacturer, downstream user or importer. The registration dossier will be sent to the then newly constituted European Chemicals Agency for a completeness check, who will forward the same to the member states.

Evaluation provides confidence that industry is meeting its obligations and prevents unnecessary testing. Evaluation is the prerogative of the designated Competent Authority in each member EU state. The competent authority will deliberate on the registration dossier which will be sent to them by the European Chemicals Agency. The Competent Authority in each Member State is also permitted to undertake substance evaluation whenever it deems fit.

Risks associated with the uses of substances of very high concern will be reviewed and, if they are properly controlled, or if the socio-economic benefits outweigh the risks and there are no safer alternatives available, then the uses will be granted an **A**uthorisation. This applies to chemicals of concern such as those on the Persistent Organic Pollutants (POPs) list, PBT list, CMR list and vPvBT list of chemicals.

The Restrictions procedure provides a safety net to manage risks that have not been adequately addressed by another part of the REACH system. A dossier on restriction is prepared by a member state or the Commission but serves across the Community.

Chemical Safety Report

The REACH program envisages creation of a chemical safety report by the manufacturer or importer of a given chemical into the EU. The chemical safety assessment shall be conducted for all substances subject to registration if the registrant manufactures or imports such a substance in quantities of 10 tonnes or more per year. The exposure scenarios envisaged in the report relevant to the downstream users will be included in an annex to the safety data sheet (SDS).

The World Largest Chemical Market, India Biggest Export Destination

The European Union is the world's largest chemical market and the impact is expected to have global ramifications both on chemical movements and chemical policy. It is India's largest export destination for chemicals (European Chemical Bureau Report).

Minimizing tests, maximizing results

To minimize extensive testing three strategies have been put into place under the REACH program.

The European Union has set up a Joint Research Center at Ispra, Italy. A special cell called ECVAM (European Center for the Validation of Alternate Methods) looks into the development of alternate methods to avoid animal testing. As an example of this one may refer to the EpiDerm/EPISKIN[®] protocol that is likely to replace the requirement for animal skin testing such as the draize test.[\(3\)](#)

The second strategy to decrease duplicate testing, especially animal testing, is the Substance Information Exchange Forum (SIEF). The information generated by the first applicant or representative of the first applicants can be shared with fresh applicants for a given fee. The Agency may intervene in case of refusal of information from the original applicant.

The third strategy is to use Quantitative Structure Activity Relationships (Q)SAR to predict the properties of a given set of chemicals through the use of robust models that may be acceptable to the Commission or the Agency.

COST IMPACTS

The REACH program has two types of cost impacts. There is the cost of testing and registration, which is the direct costs. There are also indirect costs of the program those passed on to 'downstream' users such as carmakers.

The last published business impact assessment by the EU was conducted by Risk & Policy Analysts Limited, UK in October 2003[\(4a\)](#).

Salient features of the study are as below:

- The Commission's Impact Assessment estimates the direct costs of REACH to the chemicals industry at a total of some €2.3 billion over an 11 year period, including fees to the Agency of €0.3 billion.
- Costs to downstream users: The costs to downstream users of chemicals are estimated at €2.8-3.6 billion if the market behaves as expected with a certain degree of substances withdrawn because continued production would not be profitable.

- Costs could rise to €4.0-5.2 billion if industry faces higher supply chain adaptation costs. These estimates include the direct costs passed on from the chemicals sector to downstream users.
- Total costs: The overall costs to the chemicals industry and its downstream users would then be €2.8-5.2 billion. From a macroeconomic perspective, the overall impact in terms of the reduction in the EU's Gross Domestic Product (GDP) is expected to be very limited.
- The annual turnover of European Chemical industry in 2000 was estimated at EU417 billion.

Table 1: Total Costs on REACH program net present value.

Net Present at 3% discount factor		
Euros billion	Lower Estimate	Upper Estimate
Normal Expectation	2.8	3.6
Higher substitution cost	4	5.2
Includes cost passed on to downstream manufacturers		

Table 2: Estimated number of chemicals, due to undergo testing in the European Union. As per the *current plan* there is intended to be more than one registration per product, depending on the number of producers and importers of the said chemical.

Category	from MT	to MT	Timelines yrs	Number of substance	Status in timeframe
General	1000+		3	2,704	Register
General	100	1000	6	2,461	Register
General	10	100	11	4,977	Register
General	1	10	11	17500	Register
Intermediates (Type 3)	1000+			1,700	Limited registration
Non-isolated intermediates				0	exempt
Polymers				0	Exempt
R&D				0	exempt 5 yrs
Total				29,342	

A more recent cost analysis of REACH was commissioned by Nordic Countries through Tufts University. (4b) The results are as given in Table 3. The basic costs of REACH have been estimated at EU 3.46 billion instead of the initial EU2.3 billion.

Table 3: Direct cost based on estimated average usage in the 11 year period from entry in force (eif), discounted to the present value. (Tufts University Study)

Direct Cost EU million	1-10T	10-100T	100-1000T	>1000T	Total
Testing	110	203	978	1,712	3,003
Registration	152	66	84	155	457
11 year total	262	269	1,062	1,867	3,460

QSAR economic and other benefits

Early reports in May 2003 estimated that the use of intelligent testing strategies based on (Q)SARs, the read-across approach and other waiving possibilities could result in a cost saving to industry of up to 1.2 billion Euro. (May 2003 Report to the Commission)

The most recent *available* assessment of the business impact(4a) of the new regulation on the chemical sector, including an estimation of costs for testing, was carried out for the Commissions Enterprise Directorate General (DG), “revealing figures of approximately 2.99-3.60 billion Euro, depending on whether it is assumed that there will be no or limited acceptance of (Q)SAR estimates”. (JRC website-January 2005). However, it must be noted that in the actual report summary the use of QSARs as a total replacement to testing was described as uncertain, at least unto 7 years eif. (4a)

A more recent report indicated that “1.3-1.9 million test animals could be saved, depending on the extent to which (Q)SARs are accepted. Of the total amount of animals that could potentially be used under REACH, 72% would be required for performing two-generation reproductive toxicity studies, developmental toxicity studies and in vivo mutagenicity studies.”(4c)

More extensive business impact studies are expected in early 2005 (Sacconi’s Environment Committee Report/Lena Ek’s Industry Committee Report) (2a)

QSAR APPLICATION AREAS

(Q)SAR will be used both as a supplement to chemical testing and as a replacement to testing. As a supplement to testing (Q)SAR will set up the priority tests for certain classes of chemicals, indicate in-depth testing levels that may be required, provide mechanistic interpretation of data and indicate where experimental data needs to be revalidated.

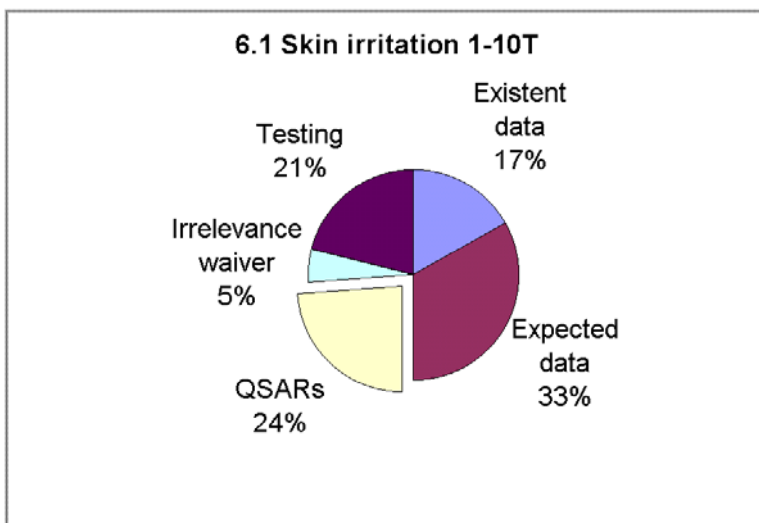
Decision trees incorporating this concept have already been developed by ECVAM. This will make the use of (Q)SARs almost mandatory even where the data ultimately submitted is experimental.(3)

But (Q)SARs also will be used to replace tests completely.(5) This will be especially true for smaller volume chemicals. Certain categories of tests have a high potential for the use of (Q)SARs. Table 4 below shows the extent of expected application of (Q)SARs as a replacement to testing. This is of course a small subset of the application areas of (Q)SARs.

Table 4: Application of (Q)SAR models under the REACH program(6)

Test Number	Test description	1-10T	10-100T	100-1000T	>1000T
5.8	Log Pow	36%	36%	36%	36%
6.1	Skin Irritation/corrosion	24%			
6.1.1	In vivo skin irritation		9%	2%	
6.2	Eye irritation	10%			
6.2.1	In vivo eye irritation		4%	1%	
6.3	Skin sensitization	28%	14%	3%	1%
6.4.1	Gene mutation bacterial	24%	9%	2%	1%
6.4.2	Cytogenicity mammalian cells	24%	9%	2%	1%
6.5.1	Acute Oral Toxicity		4%	1%	
6.5.2	Acute Inhalation		8%	2%	
6.5.3	Acute dermal	8%	2%		
6.6.1	Short term repeated		4%	1%	
6.6.2	sub chronic		10%	2%	1%
6.6.3	Long term repeated tox				1%
6.7.1	Developmental toxicity screening		4%	1%	
6.7.2	Developmental toxicity test		5%	1%	
7.1.1	short term daphnia	32%	14%	3%	1%
7.1.2	Growth inhibition algae	40%	20%	5%	1%
7.1.3	Short term fish		14%	3%	1%
7.1.5	Long term daphnia	24%	12%	3%	1%
7.1.6	Long term fish		12%	3%	1%
7.2.1.1	Ready biodeg	24%	9%	2%	1%
7.2.2.1	Hydrolysis		10%	2%	1%
7.3.1	Adsorption/desorption		20%	5%	3%

Figure 1: As an interpretation of Table 4, shown below is the break-up of data expected by registration numbers for the Skin Test in the 1-10T bracket, showing that 24% of the registrations will quote the data through (Q)SARs.



Base dataset for accurate determination of properties and activity of chemicals

QSAR studies depend on reliable and collated experimental data in order to develop accurate predictive models.

One US study, Toxic Ignorance, prepared by the Environmental Defense Fund (EDF), raised a variety of concerns about the untested chemicals which are manufactured and imported into the U.S. It found that baseline data on health effects were not publicly available for many high production volume chemicals. EPA prepared its own study, titled the Chemical Hazard Data Availability Study, which found similar results and reinforced the need for government leadership on this issue. Echoes of these studies found reverberations throughout the world.

The OECD countries which includes the USA, EU, and Japan have undertaken programs to assess the impact of commercial chemicals in their High Production Volume Chemicals Program. [\(7a\)](#) The US through their HPV Challenge Program has raced ahead and compiled robust literature data on nearly 1500 chemicals. [\(7b\)](#) The information database is now structured and peer reviewed, perhaps for the first time in history. Test programs have been devised to fill in the gaps in information. Similarly the EU has drawn robust summaries on high volume chemicals through the IUCLID programs. [\(7c\)](#) The UN GHS program, which is implementable by 2008 globally, calls for a certain minimal degree of chemical testing including environmental testing. [\(7d\)](#) We must thus expect the database on chemical information to improve in the years to come. This database forms the base set data for the development of (Q)SAR models.

QSAR MODEL VALIDATION

The regulatory bodies such as OECD, EPA and the European Commission have developed criteria to assess rigorous models. By and large the OECD criteria for a rigorous (Q)SAR model has been accepted under the REACH program. [\(8\)](#)

The four Principles developed by OECD for Assessment of a Robust QSAR model are

- 1) A defined endpoint
- 2) An unambiguous algorithm
- 3) A defined domain of applicability
- 4) Appropriate measures of goodness-of-fit, robustness and predictivity
- 5) A mechanistic interpretation, if possible

Survey Reports on Existent QSAR models:

An OECD web page, which may be readily consulted, surveys, lists and categorizes (Q)SAR models that may be used for regulatory purposes. [\(9\)](#)

Joint Research Center (JRC) QSAR cell:

The European Commission under REACH has created a cell in the Joint Research Center (JRC) at Ispra Italy with the mission to develop the “Framework for the independent development, validation and dissemination of QSARs”. The JRC expects to take the learning experience from QSARs further afield and “adapt future REACH developed QSAR in Cosmetics Directive, the Biocidal Products Directive and the Plant Protection Products Directive”.

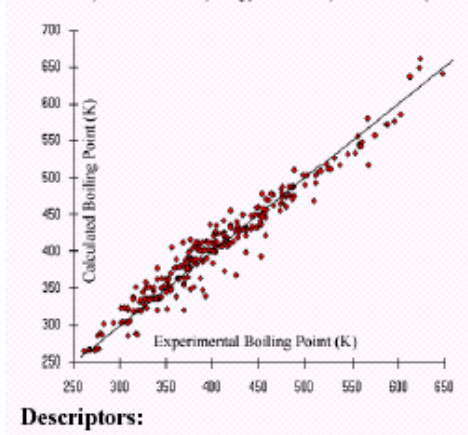
QSAR success stories

QSAR models are routinely used in several areas of pharmaceutical development. It has had notable success in development of drugs such as Norfloxacin(10a) and Zolmitriptan(10b). Even though (Q)SAR have still to be widely accepted for regulatory purposes (11,3) as the primary source of a given property, their use is fairly common in conjunction with property data. Some models however have already been developed and are known to be fairly accurate. This may be seen from the flash point estimates given below from Dr. Alan Katritzky's group(12). Flash points form what is called a base set parameter. Even here QSAR will be used by almost every laboratory before submission of an experimental test result.

Figure 2: Ref.: Katritzky A. R.; Petrukhin R.; Jain R.; Karelson M. "QSPR Analysis of Flash Points", J. Chem. Inf. Comp. Sci., 41 (2001) 1521-1530.

Statistical characteristics:

$n = 298$, $R^2 = 0.954$, $R^2_{cv} = 0.953$, $F = 3030$, $s = 16.15$



Descriptors:

1. cubic root of the gravitation index
2. hydrogen donor charged surface area

Indian Response

In response to global regulatory programs such as REACH the Ministry of Chemicals & Fertilizers in conjunction with the Indian Chemical Manufacturers Association (ICMA) has formed three sub-group task forces.

- 1) The first task force looks at the framework needed by India to respond to the global regulatory programs. This includes setting official responses and views from India. It will also co-ordinate the activities of other task forces.
- 2) The second task force looks at the development of GLP laboratories throughout India.
- 3) The third task force seeks to develop India as a hub for IT based Services under REACH.

Vision Of The Task Force

To help India meet and capitalize on the advantage of developing IT based services under Global Regulatory Programs such as REACH, including the promotion and development of QSAR models, by co-ordination and development of the expert capabilities in the country.

MISSION STATEMENT

The task force will be looking into the following aspects. Details on the activities and implications will be treated later.

- 1) Catalyze the development of cost effective and regulatory acceptable QSAR models in India by leveraging India's IT strengths and technical scientific expertise.
- 2) Attract entrepreneurship to the area. Promote (Q)SAR models developed in India.
- 3) Co-ordination with the GLP Laboratories in the use of QSAR models for decision making.
- 4) Any other IT based opportunity that may arise including as may be required by other groups.
- 5) Developing a database of experts and expertise, on QSAR and other computational techniques, available in India.

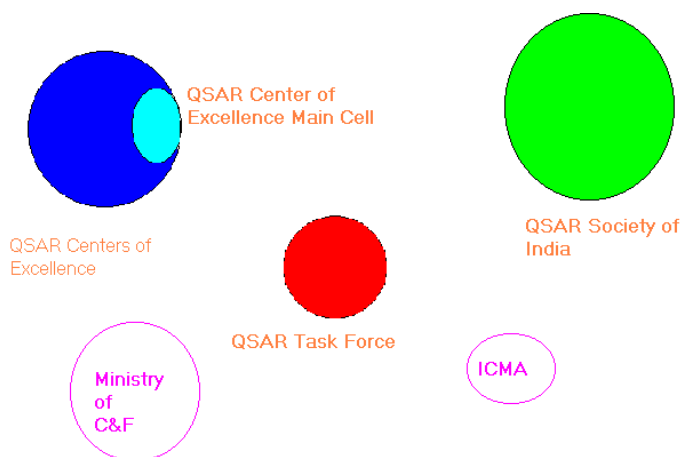
What may be required under Mission plan in IT initiatives other than QSAR

1. A structured format which clearly delineates the endpoints required by testing under REACH in various categories. This will help quickly analyze which endpoints would need to be tested further. It will help QSAR development by clear definition of the data domain status. It will help other GLP efforts being the format required for Registration for a Regulatory Process.
2. Maintaining a database of QSAR and REACH experts and expertise in India.

STRUCTURES ENVISAGED

This paper seeks the creation of the following structures to support the initiative

Figure 3: Structures created to support the Task Force created through the coordinated efforts of the Ministry Of Chemicals And Fertilizers and The Indian Chemical Manufacturers Association (ICMA).



Centers of Excellence

An important structure envisaged is the creation of Centers of Excellence both in the private sector and using the Government network of laboratories. Coordination with GLP

Laboratories is important since it is expected that QSARs will be used regularly by them to validate literature/experimental data and to take decisions on priority testing. Primarily the paper recognizes that the main expertise in (Q)SAR today is with the pharmaceutical and biochemistry sector. Because of its nature this will continue to attract the best QSAR talent in India for some time. It is important that the regulatory applications be co-ordinated with the QSAR initiatives in other areas. Companies which are already undertaking QSAR studies may be persuaded to undertake and understand QSAR application in the Regulatory Area. An important aspect is that whereas entities emerging from (Q)SARs developed in the pharmaceutical sector are screened out at a high attrition rate those used for regulatory purpose do not have this screening out possibility. Members from the (Q)SAR centers of excellence will also be on the panel of the Task Force.

(Q)SAR Society

It is important to also have a grassroots initiative on QSARs. Hence a database on QSAR capabilities both in academics and in the private will be created. Interaction among members will be encouraged through seminars. A special emphasis at these seminars will be the regulatory aspect, but to attract a wider audience pharmaceutical and agrochemical applications will be part of the initiative. Hopefully this will culminate in the formation of a QSAR Society with regular bulletin boards, seminars and even perhaps magazine space. The Task Force will restrict itself only to a catalytic role.

(Q)SAR Task Force

The QSAR Task Force would however continue to work on the regulatory aspect alone. Initially its membership will be by appointment but later a charter may be drawn up to constitute its membership. It may be later renamed as the (Q)SAR Cell for Regulatory purposes.

- It will have the mission plan as outlined earlier.
- It will help create the framework as described above.
- It will catalyze the development of QSARs through the pathway described below.
- It will encourage development of valid QSAR models through adoption and adaptation of a robust set of principles such as that developed under OECD.
- It will help promotion of QSARs developed in India through creation of a hub and survey reports.
- It will also at various periods of time undertake positional papers to help promote and develop QSAR as given in the mission plan.

The Path Forward

The major milestones for developing the framework suggested is as below.

- 1) White Paper and consultative period.
 - a) A release date of January 31st 2005 is envisaged.
 - b) The consultative period for addressing suggestions and criticisms is unto February 15th, 2005.
- 2) Creation of the Task Force
 - a) A meeting of the Task Force chaired by Mr.S.N.Singh-Head “IT Initiative Task Force for Global Regulatory Programs” is scheduled for February 21st, 2005.

- b) The members of the initial task force in the formation period are by appointment by The Ministry of Chemicals and Fertilizers and ICMA.
- 3) Create an information database on current India QSAR capability and scout talent in the area.
 - a) An initial database would be compiled by February 15th, 2005.
 - b) The suggestions on the fields of the database would be accepted during the consultative period.
 - c) The database will be continuously upgraded.
- 4) Create an awareness of the opportunity.
 - a) It is suggested that a (Q)SAR seminar be held in the country. A special emphasis would be on QSAR for Regulatory Aspects. The decision on this could be initiated on February 21st.
 - b) Depending on the success of the seminar a QSAR Society may be launched. This will be a source of information on the database. The Head of the QSAR Society should be preferably an academic with QSAR background. The activities are to be defined by the Society and will be beyond the purview of the task force.
- 5) Understanding of Regulatory and Environmental QSAR models is important. Three studies are considered important.
 - a) A detailed study of the economic impact of QSAR models used in Regulatory Applications and the likely future scenario globally.
 - b) An understanding of the chemical domains of importance to India's export and those where QSAR models would be important. Some of the globally important models may be purchased for immediate use in GLP laboratories. Several models are such that they may be tweaked to improve their domain applicability. There will be an immediate need of such models for assistance to the GLP laboratories.
 - c) Some endpoints may be effectively simulated and determined in India based on Indian capabilities including capabilities being developed in GLP Laboratories. The QSAR angle may exploit the endpoint capability.
- 8) Directly interact with QSAR Groups and relevant regulatory authorities to understand how to fine tune the program and the scope for Indian entry.
- 9) Catalyse the formation of Centers of excellence.
 - a) Understand how Indian cells working on QSARs can be converted to Centers of excellence-the hardware, people and software requirements.
- 10) Adopt and adapt a QSAR validating process.
 - a) Currently the OECD models may be adapted. To adapt this a study of the validation process needs to be done.
 - b) One must watch for further developments at the OECD, EU JRC and US-EPA.
- 11) Promotion of (Q)SAR models from India
 - a) A survey report can be created and published in a magazine (Including the ICMA flagship magazine) on any (Q)SAR model so far developed.. It needs to explain in a structured manner such as available on the OECD website the applicability, domain, robustness and endpoint of a model. Also factors like which company can be contacted for sale. Later as and when more models are developed a hub may be created.
- 12) Choose a parameter, which India can test and which is amenable to QSAR. Develop a model for the parameter. Generate an information database. Test the model with the

help of data from GLP Labs. Submit the validated model for promotion. This will need study 5 c) as a prerequisite.

- 13) Develop with the help of the GLP Labs a robust literature study of a chemical portfolio of an Indian company as per study 5 b). Use this database to predict certain endpoints for fine volume chemicals of export interest. Help submit the data for regulatory submission.

