Regulatory Affairs Made Easy

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Obtaining suitable data to support regulatory submissions

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FS 553614

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Why do we need data?

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Essentially because we need to know how to best protect man and the environment from hazardous chemicals!!

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History – "The GHS"

- Earth Summit, Rio de Janeiro in 1992 ; World Summit, Johannesburg in 2002 recognised this as an important global issue.
- Tasked the United Nations to develop a 'Globally Harmonised System' (GHS) on classification and labelling.
- The GHS is a single worldwide system for classifying and communicating the hazardous properties of industrial and consumer chemicals. Sits alongside the UN 'Transport of Dangerous Goods' system.
- **UN GHS is not a formal treaty**, but instead is a non-legally binding international agreement. Therefore countries (or trading blocks) must create local or national legislation to implement the GHS.
- GHS also aims to provide a structure for countries that do not yet have a classification and labelling system.

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Adoption of “GHS”

A Slow Process !

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What it means…….

Countries have implemented ways and means of determining chemical hazards and associated risks, usually via some form of formal notification requirement.

Different requirements, based on whether a chemical is “new” or “existing”. But…. general perception that prior/ existing regulations were not adequate,

Most hazard schemes now are based upon GHS in the global areas where developed chemical industries are present.

What it means…….

But……

Just because they have a scheme does not mean that the data requirements are always the same - regardless of GHS!!!

Worldwide Chemical Schemes

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Current Schemes

- Europe – REACH
- Japan – JCSCL and ISHL
- Korea – K-REACH
- Canada – CEPA
- Switzerland – Chem O
- Australia – NICNAS (reforms?)
- New Zealand – ERMA
- China – SCC-MEP (reforms?)
- USA – TSCA notification (reforms?)
- Philippines – PICCS (reforms?)
- Taiwan – TSCSA (reforms?)
- Turkey – KKDIK
- Malaysia – CLASS (reforms?)

Upcoming Schemes.

- UK – “UK REACH”
- Thailand
- Vietnam
- Indonesia
- India
- Myanmar , Cambodia, Laos
- Argentina
- Brazil
- Colombia
- Chile
- Kazakhstan
- Russia “REACH”

There will be others……

All of which (will) need data to support your application!

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Could the same data be used globally?

- **Yes and No!**
- **To file a chemical substance notification in any scheme, you will need physicochemical, toxicological and eco-toxicological / environmental fate data.**
- **Actual data requirement depends on your tonnage level.**
- **In reality, the data requirements in different countries/regions are not the same.**
- **However, the data requirements share many common similarities.**
- **If a region has extra requirements, you will need to supplement with extra data.**
- **Take into consideration alternative methods in different countries, requirements for GLP studies as well as the registration requirements for polymers.**

So where to start?

First….

What are the predicted markets?

And how much?

Most schemes requirements are tonnage dependent.

Be realistic – you can always upgrade!

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So where to start?

Then….

You going to want to make a shopping list.

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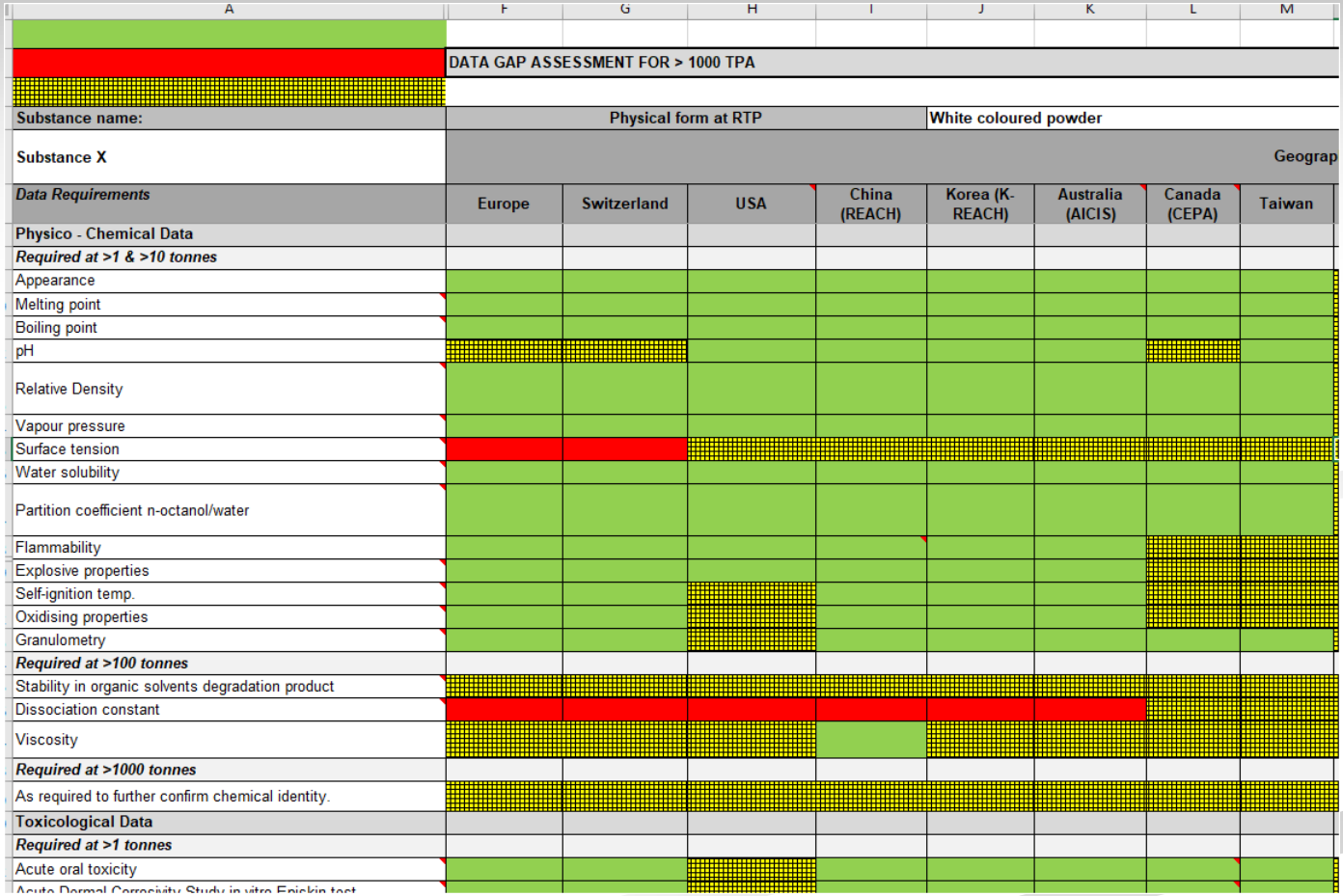
Data Gap Analysis

Your shopping list is the "Data Gap Analysis".

Start by identifying data requirements by region.

Identify any "country specific" requirements, e.g Polymer vs monomer requirements



DATA GAP ASSESSMENT FOR > 1000 TPA

Substance name:	Physical form at RTP				White coloured powder			
Substance X								Geograp
Data Requirements	Europe	Switzerland	USA	China (REACH)	Korea (K-REACH)	Australia (AICIS)	Canada (CEPA)	Taiwan
Physico - Chemical Data								
Required at >1 & >10 tonnes								
Appearance								
Melting point								
Boiling point								
pH								
Relative Density								
Vapour pressure								
Surface tension								
Water solubility								
Partition coefficient n-octanol/water								
Flammability								
Explosive properties								
Self-ignition temp.								
Oxidising properties								
Granulometry								
Required at >100 tonnes								
Stability in organic solvents degradation product								
Dissociation constant								
Viscosity								
Required at >1000 tonnes								
As required to further confirm chemical identity.								
Toxicological Data								
Required at >1 tonnes								
Acute oral toxicity								
Acute Dermal Corrosivity Study in vitro Episkin test								

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Data Gap Analysis

Substance name:	CAS	Substance name			Notes
Substance X	1234-56-7	Substance X			
Data Requirements	OECD Number	Current indicative lab costs	No. of Studies required	Cost Euro	
Physico - Chemical Data					
Required at >1 & >10 tonnes					
Appearance	N/A	EUR 0	1	EUR 0	Study available.
Melting point	OECD 102	EUR 1,410	1	EUR 1,410	Conduct
Boiling point	OECD 103	EUR 780	1	EUR 780	Conduct
pH	N/A	EUR 0	1	EUR 0	Non-GLP brief assessment is acceptable.
Relative Density	OECD 109	EUR 1,045	1	EUR 1,045	Conduct
Vapour pressure	OECD 104	EUR 4,730	1	EUR 4,730	Study available.
Surface tension	OECD 115	EUR 1,170	1	EUR 1,170	Dependant on outcome of water solubility; can be waived if < 1 mg/l
Water solubility	OECD 105	EUR 5,210	1	EUR 5,210	Study available.
Partition coefficient n-octanol/water	OECD 117 / 107	EUR 9,800	1	EUR 9,800	Conduct
Flammability	EU A10	EUR 725	1	EUR 725	Study available.
Explosive properties	EU 14	EUR 385	1	EUR 385	Waiver On basis that no structures indicative of explosive properties available
Self-ignition temp.	EU A15	EUR 3,210	1	EUR 3,210	Conduct
Oxidising properties	EU A17	EUR 385	1	EUR 385	Waiver On basis that no structures indicative of oxidising properties available.
Granulometry	OECD 110	EUR 3,675	1	EUR 3,675	Study available.
Required at >100 tonnes					
Stability in organic solvents degradation product	None	EUR 2,000	0	EUR 0	Waiver; stability is not considered to be critical
Dissociation constant	OECD 112	EUR 5,500	1	EUR 5,500	Potentially waiver if water solubility is < 1 mg/l
Viscosity	OECD 114	EUR 2,500	0	EUR 0	Waiver; solid.
Required at >1000 tonnes			Total	EUR 38,025	
As required to further confirm chemical identity.	Variable	Variable	0	EUR 0	Not required.
Toxicological Data					
Required at >1 tonnes					
Acute oral toxicity	OECD 423	EUR 1,960	1	EUR 1,960	Conduct
Acute Dermal Corrosivity Study in vitro Episkin test	OECD 431	EUR 2,940	1	EUR 2,940	In progress

Then add in what data you already have available in the organisation.

Useful for budgeting as well!

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Sources of data

Once "missing" data is identified, then you are ready to start gathering what you need.

Sources of potential data fulfillment:

- **Internet – search engines for published studies and literature.**
- **Study data.**
- **Read across and Grouping**
- **Quantitative Structure Activity Relationships – QSAR**
- **Waivers**

Use of alternative methods and all other options are generally built into country specific legislation.

All can be potentially be used, but certain types can be rejected, dependent on the region.

Internet – search engines

There is a lot of historical data studies available out there and the advent of the internet means that accessing this valuable resource is a lot easier than it was 10 years ago. However, to find relevant data, you need to know where to look.

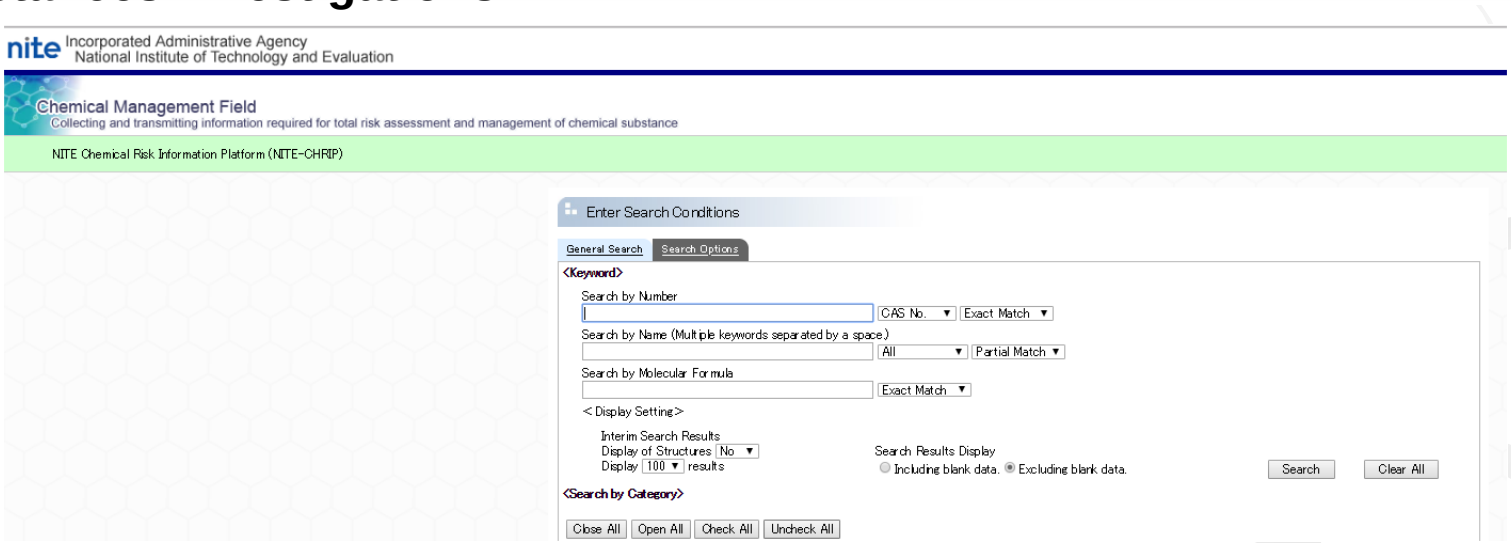
You can search:

- **Worldwide inventories**
- **Specific information sites**
- **Commercial organisations.**

Internet – search engines

Worldwide inventories

Some inventories publish reports on their database, e.g from Existing Substances investigations:



e.g Japan NITE database:

Internet – search engines

Worldwide inventories

ECHA Disseminated Dossier Website

Internet – search engines

Specific information sites

There are specific information sites for endpoints, for example:

- **Hazardous Substances Data Bank (HSDB)**
- **Toxicology Literature Online (TOXLINE)**
- **Chemical Carcinogenesis Research Information System (CCRIS)**
- **Developmental and Reproductive Toxicology Database (DART)**
- **Genetic Toxicology Data Bank (GENE-TOX)**
- **International Agency for Research on Cancer (IARC)**
- **International Toxicity Estimates for Risk (ITER)**

Free searching facilities here; but often contain limited information from original literature sources and little information on test information quality.

Generally use these as an assessment of the amount of published information on a substance and as a link to the cited original sources.

Internet – search engines

Commercial organisations.

There are many organisations out there who offer search facilities, with the ability to purchase literature papers and reports directly for download.

Sources of Health and Environmental Hazard Information

Databases	Available from	File Type	Subjects Covered	Years Included
Agricola	Commercial database vendors	Bibliographic, indexed	Agriculture, pesticides, human and environmental health	1970 - present
AMA Journals	Commercial database vendors	Full text	Medicine, occupational medicine	1982 - present
Encompass Literature (previously APILIT – American Petroleum Institute)	Subscribers only, Commercial database vendors, web version	Bibliographic, extensive indexing, CAS RNs	Toxicology, environmental health, risk assessment	1963 - present
Aquaculture	Commercial database vendors	Bibliographic, indexed	Environmental, aquatic toxicology	1970 - present
Aquatic Sciences & Fisheries Abstract	Commercial database vendors	Bibliographic	Environmental, aquatic toxicology	1978 - present

Listed are available, ECHA Guidance "Chapter R.3: Information gathering" provides lists like the above.

Internet – search engines

Tips.

- **Just because its available on-line doesn't mean that you can use it freely!**
- **Perform due diligence to ensure that you aren't breaching IP or copyright. Purchase rights if you wish to use it.**
- **Assess the quality – is it detailed enough to fulfil a certain endpoint? It is possible to provide several "brief" sources that coincide to support a specific endpoint ("Weight of Evidence" approach)**
- **Record how you've searched – databases etc for reference.**

Study Data.

All authorities accept actual study reports providing it meets with their quality standards. You can use:

- **Existing In house data**
- **New Data specifically generated.**
- **Existing data, (including that not generated in accordance with the latest methods or to GLP or equivalent standards)**
- **Human specific data**

Again, important to assess the quality of data. All can be potentially be used, but certain types can be rejected, dependent on the region.

Good Laboratory Practise (GLP) is the internationally accepted laboratory management system. All countries will accept data generated by GLP Laboratories to appropriate methods, PROVIDING they recognise GLP status.

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Study Data.

Physico-chemical Data

- **Can be generated by both GLP and non-GLP accredited laboratories.**
- **If non-GLP, laboratory should have an equivalent standard that it works to (e.g ISO 17025) and associated certificate.**
- **Exception is Partition Coefficient study – this should be conducted to GLP in all cases, as some regions will not allow non-GLP methods (e.g Korea). Considered to be critical for bioaccumulation potential.**
- **Main area where in-house data is likely to be suitable and accepted.**

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Study Data.

Toxicology Data

- **Should always be generated to GLP standards.**
- **In vitro assessment of endpoints such as skin and eye irritation and sensitisation should be conducted first. Certain regions (e.g China) will only accept positive results here, so in vivo assessments should be considered in addition.**
- **Beware of country specific requirements!**
- **Existing non-GLP studies should be carefully assessed to ensure that they meet the required standard.**

Study Data.

Ecotoxicology and Environmental Fate Data

- **Should again always be generated to GLP standards.**
- **Main Area where duplication will be required. For example, Chinese notifications will require that certain studies (e.g. biodegradation, fish and Daphnia studies) are carried out in China. However, some other jurisdictions will not accept such studies conducted in China alone.**
- **Existing non-GLP studies should be carefully assessed to ensure that they meet the required standard.**

Study Data.

Human specific data

- **Really needs to be judged by an "expert" as to whether it can be used.**
- **Most are historical, such as irritation studies. There are more recent skin patch testing (for allergens etc) that are useful if you can demonstrate suitability (patch testing your own staff as part of Occupational Health exercises generally isn't a broad enough spectrum).**
- **Generally used as supporting data unless very recent and robust.**

Study Data.

Tips

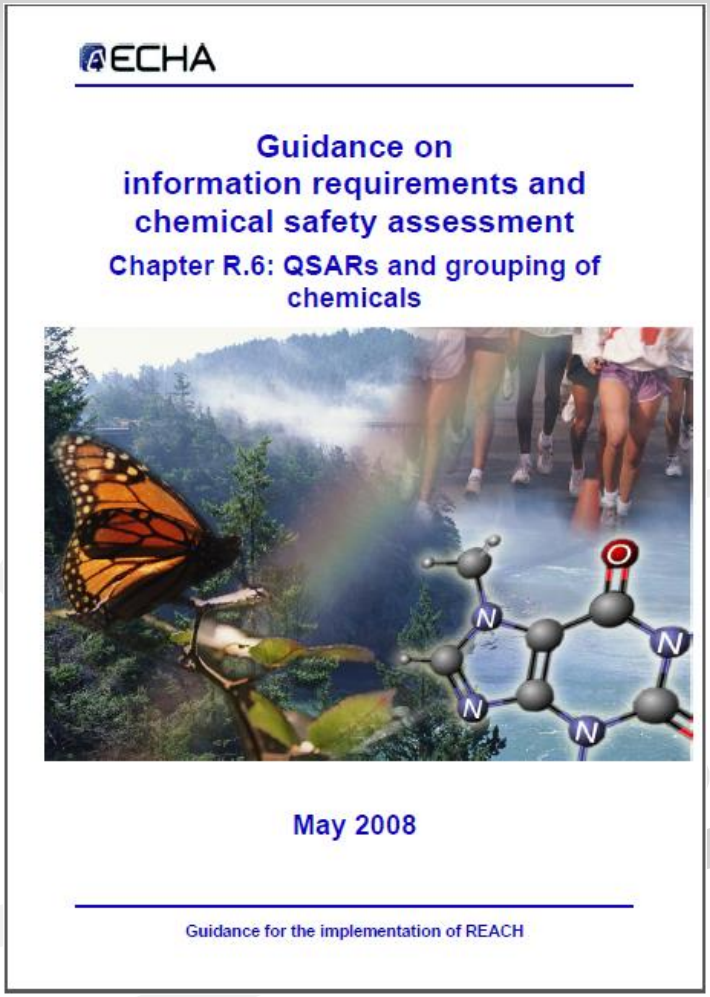
- **Check and see if someone else has already notified / registered – inquiry process; there may be data already available.**
- **Data Generation is expensive, so shop around the various labs that can do this.**
- **Get the most from your data! Ensure that the test covers as many jurisdictions as possible. E.g use Japan specific protocols for mutagenicity assessments, as these will be accepted by all other regions regulators.**
- **Ensure you understand region-specific tests – e.g polymer testing in Pacific regions is a requirement that is not covered under European REACH schemes.**
- **Test smart! Structure your approach to take advantage of waivers.**

Read across and Grouping

This is a little more difficult to use, but with sound scientific justification, most authorities will accept the use of it.

The ECHA Guidance is a good place to start, as emphasises what is required.

Also, the Read-Across Assessment Framework (RAAF) published 2017 by ECHA is a good information source, as it details what experts are looking for in their review processes.



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Read across and Grouping

Read-across is the technique for predicting endpoint information for one substance (target substance), by using data from the same endpoint from (an)other substance(s) or group of substances.

- **One-to-one – Analogue Approach.**
- **One-to-many – Analogue / Category Approach.**
- **Many-to-one - Analogue / Category Approach**
- **Many-to-many - Category Approach**

Read across and Grouping

To be effective and understood by regulators, you will need to:

- **Present your hypothesis - why is it applicable?**
- **Present your justification - demonstrate that the hypothesis is supported.**
- **Provide substance identity information on all substances included in the read-across.**
- **Outline the structural similarity(ies) between the substances**
- **Provide your conclusions**

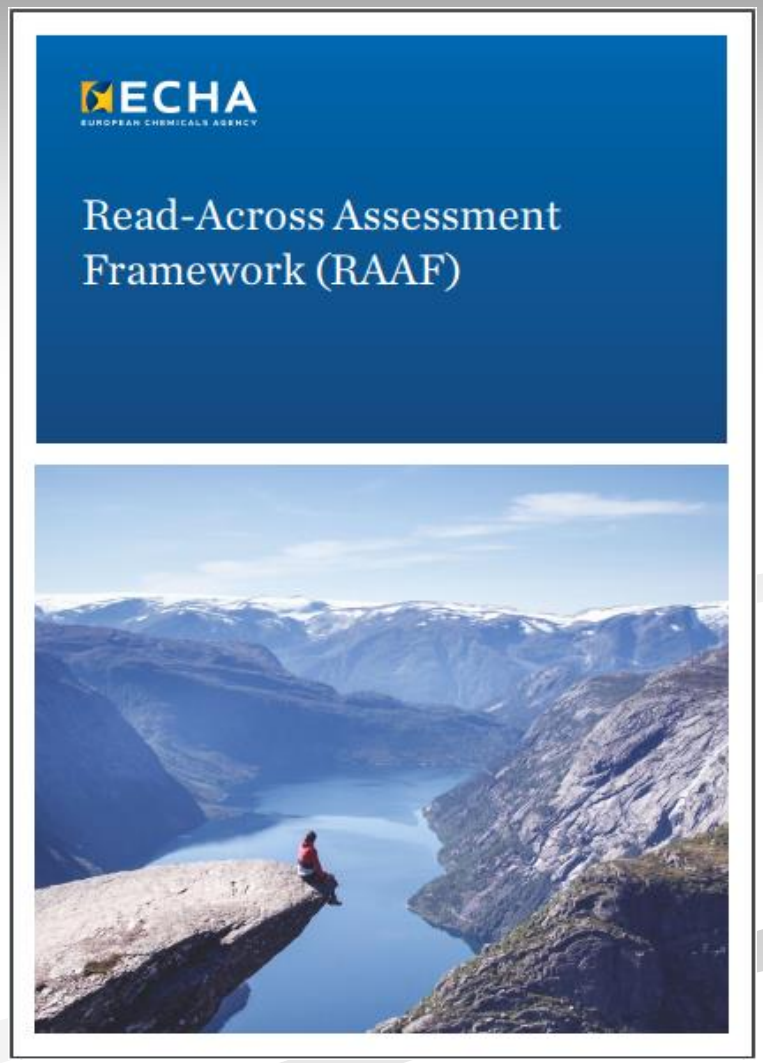
Read across and Grouping

Present your findings in an easily understood report.

Would recommend to review the RAAF document from ECHA, as this provides excellent advice.

Templates for reporting are available at

https://echa.europa.eu/support/guidance-on-reach-and-clp-implementation/formats



Read across and Grouping

Tips

- **To use Read Across / Grouping you need a strong justification that is easily understood. Regulators can reject these easily if it is not easily understood.**
- **Remember that data owners are ONLY OBLIGED to share data if they are involved in that regions scheme. There is no obligation to share data for read across purposes within any of the legal texts.**
- **Its worthwhile considering translation of your report for some regions, so that it can be understood easily (most regions accept English language study reports).**
- **For China, read-across can only be applied for serial notifications (for a group of substances). Such data generally needs to be "new" data; if it is from an existing substance, then it is likely to be rejected.**

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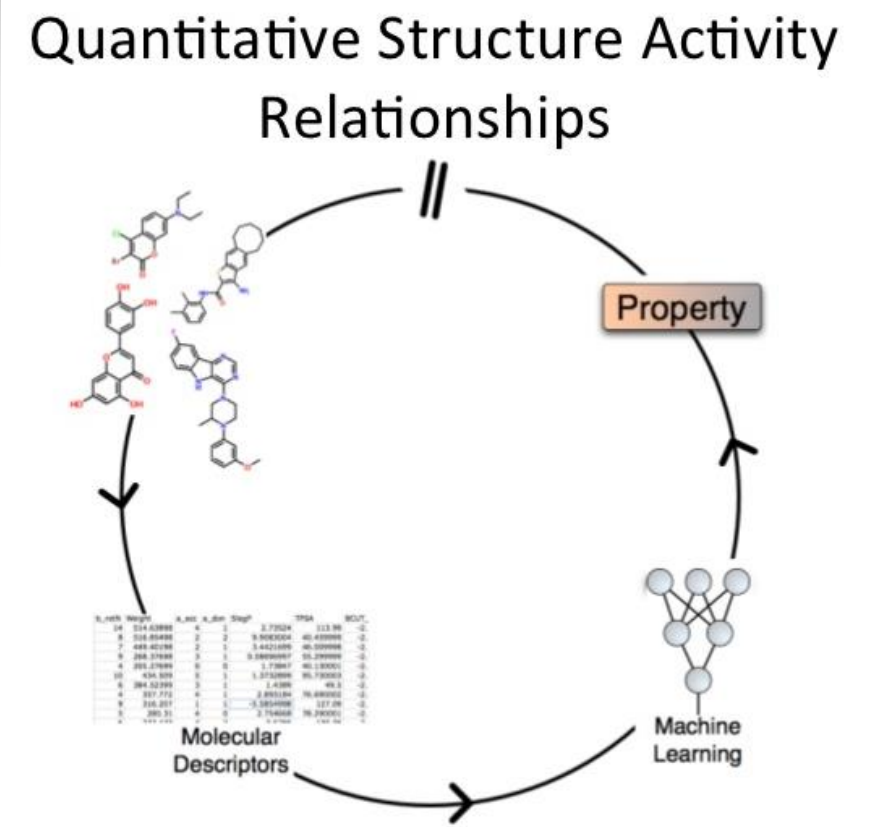
Quantitative Structure Activity Relationships – QSAR

A SAR is a qualitative relationships that relates a (sub)structure to the presence or absence of a property or activity of interest.

A QSAR is a mathematical model (often a statistical correlation) relating one or more quantitative parameters derived from chemical structure to a quantitative measure of a property or activity (e.g. a (eco)toxicological endpoint). QSARs are quantitative models yielding a continuous or categorical result.

"*In silico*" techniques!



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Quantitative Structure Activity Relationships – QSAR

QSARs can be used to replace test data, however in practice, it is foreseen that (Q)SAR information will most often be used to supplement experimental test data within chemical categories and endpoint-specific targets.

Its the future!

QSAR's are still in development, and there are a wide variety of applications available. These will improve as data becomes available, and models are developed.

As for the earlier "Internet" section, there are a variety of free models as well as commercial organisations offering systems.

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Quantitative Structure Activity Relationships – QSAR

"Free" Systems.

- Facilitates the practical application of grouping of chemicals and read-across approaches for data gap filling.
- Serves as a platform that incorporates various modules and databases from other sources.
- Is applicable to discrete organic chemicals.
- Is available free of charge

https://qsartoolbox.org/

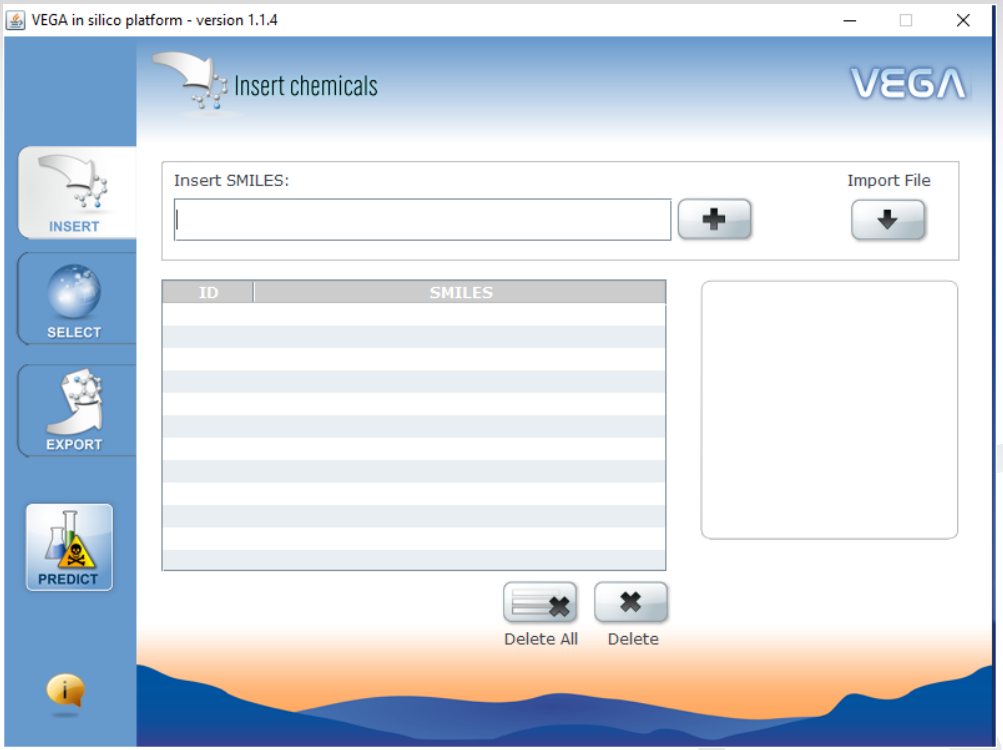
Quantitative Structure Activity Relationships – QSAR

Free Systems.

- Can assess a variety of endpoints.
- Produces rapid pdf reports.

https://www.vegahub.eu

VEGA QSAR



Quantitative Structure Activity Relationships – QSAR

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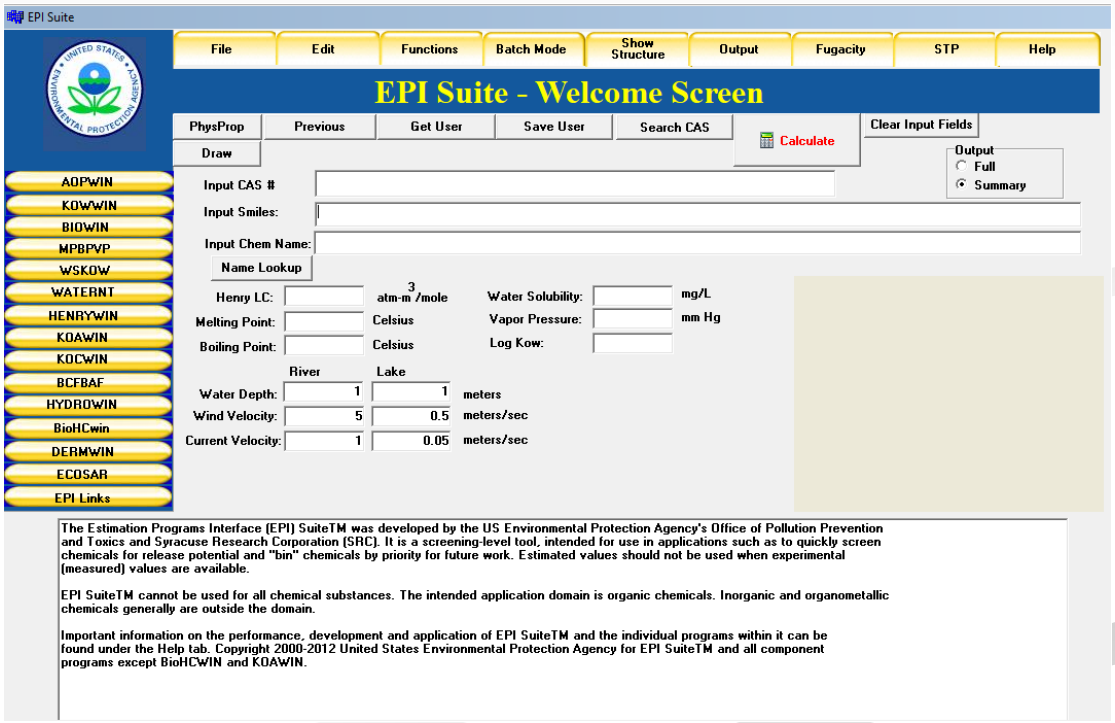
Free Systems.

EPI Suite™–Estimation Program Interface

- Can assess a variety of endpoints.

https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface#download



Quantitative Structure Activity Relationships – QSAR

Use of QSAR's.

In an ideal situation, QSAR results can be used on their own for regulatory purposes if they are considered relevant, reliable and adequate for the purpose, and if they are validated in an appropriate manner.

In reality, they tend to be favoured more in a "supporting" role.

In order for a (Q)SAR result to be adequate for a given regulatory purpose, the following conditions must be fulfilled:

1. the estimate should be generated by a valid (relevant and reliable) model

2. the model should be applicable to the chemical of interest with the necessary level of reliability

3. the model endpoint should be relevant for the regulatory purpose

Document validity using the:

- **QSAR Model Reporting Format (QMRF)**
- **QSAR Prediction Reporting Format (QPRF)**

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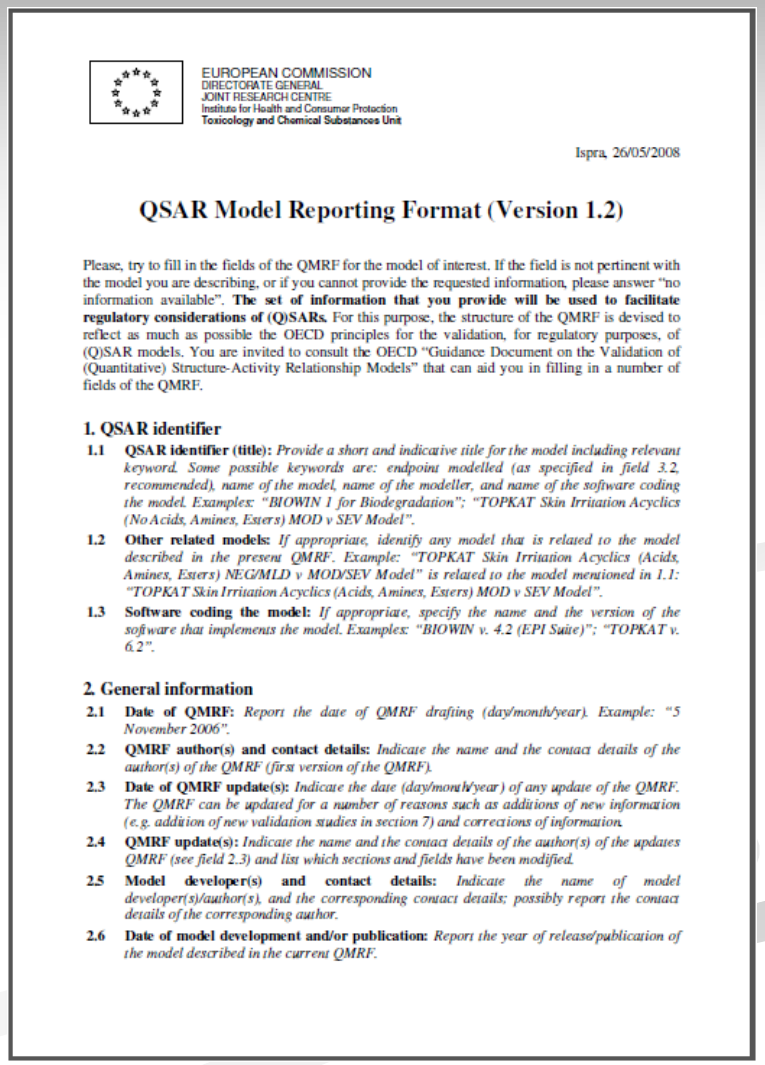
Quantitative Structure Activity Relationships – QSAR

Use of QSAR's.

QMRF

This should involve an input from the developer(s) and/or proponent of the model, as well as information from any evaluation studies performed with the model. Such documents are available on line.



EUROPEAN COMMISSION
DIRECTORATE GENERAL
JOINT RESEARCH CENTRE
Institute for Health and Consumer Protection
Toxicology and Chemical Substances Unit

Ispra, 26/05/2008

QSAR Model Reporting Format (Version 1.2)

Please, try to fill in the fields of the QMRF for the model of interest. If the field is not pertinent with the model you are describing, or if you cannot provide the requested information, please answer "no information available". **The set of information that you provide will be used to facilitate regulatory considerations of (Q)SARs.** For this purpose, the structure of the QMRF is devised to reflect as much as possible the OECD principles for the validation, for regulatory purposes, of (Q)SAR models. You are invited to consult the OECD "Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship Models" that can aid you in filling in a number of fields of the QMRF.

1. QSAR identifier

1.1 **QSAR identifier (title):** *Provide a short and indicative title for the model including relevant keyword. Some possible keywords are: endpoint modelled (as specified in field 3.2, recommended), name of the model, name of the modeller, and name of the software coding the model. Examples: "BIOWIN 1 for Biodegradation"; "TOPKAT Skin Irritation Acyclics (No Acids, Amines, Esters) MOD v SEV Model".*

1.2 **Other related models:** *If appropriate, identify any model that is related to the model described in the present QMRF. Example: "TOPKAT Skin Irritation Acyclics (Acids, Amines, Esters) NEG/MLD v MOD/SEV Model" is related to the model mentioned in 1.1: "TOPKAT Skin Irritation Acyclics (Acids, Amines, Esters) MOD v SEV Model".*

1.3 **Software coding the model:** *If appropriate, specify the name and the version of the software that implements the model. Examples: "BIOWIN v. 4.2 (EPI Suite)"; "TOPKAT v. 6.2".*

2. General information

2.1 **Date of QMRF:** *Report the date of QMRF drafting (day/month/year). Example: "5 November 2006".*

2.2 **QMRF author(s) and contact details:** *Indicate the name and the contact details of the author(s) of the QMRF (first version of the QMRF).*

2.3 **Date of QMRF update(s):** *Indicate the date (day/month/year) of any update of the QMRF. The QMRF can be updated for a number of reasons such as additions of new information (e.g. addition of new validation studies in section 7) and corrections of information.*

2.4 **QMRF update(s):** *Indicate the name and the contact details of the author(s) of the updates QMRF (see field 2.3) and list which sections and fields have been modified.*

2.5 **Model developer(s) and contact details:** *Indicate the name of model developer(s)/author(s), and the corresponding contact details; possibly report the contact details of the corresponding author.*

2.6 **Date of model development and/or publication:** *Report the year of release/publication of the model described in the current QMRF.*

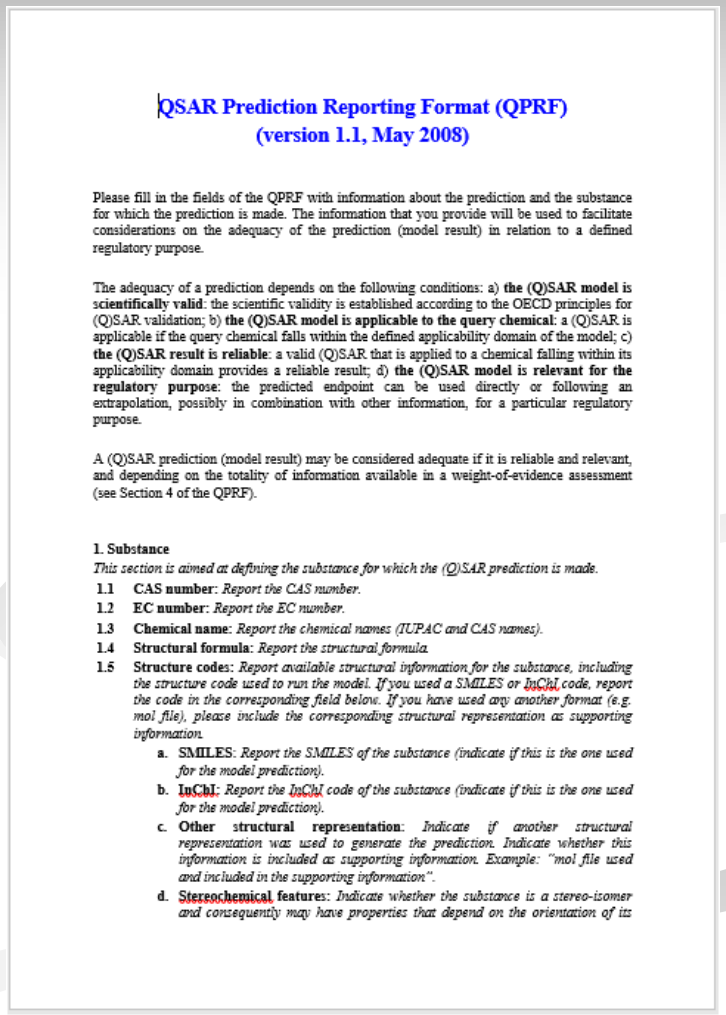
Quantitative Structure Activity Relationships – QSAR

Use of QSAR's.

QPRF

This should explain how an estimate has been derived by applying a specific model or method to a specific substance. It should include information on the model prediction(s), including the endpoint, a precise identification of the substance modelled, the relationship between the modelled substance and the defined applicability domain, and the identities of close analogues.

Needs to be completed by the user.



QSAR Prediction Reporting Format (QPRF)
(version 1.1, May 2008)

Please fill in the fields of the QPRF with information about the prediction and the substance for which the prediction is made. The information that you provide will be used to facilitate considerations on the adequacy of the prediction (model result) in relation to a defined regulatory purpose.

The adequacy of a prediction depends on the following conditions: a) **the (Q)SAR model is scientifically valid**: the scientific validity is established according to the OECD principles for (Q)SAR validation; b) **the (Q)SAR model is applicable to the query chemical**: a (Q)SAR is applicable if the query chemical falls within the defined applicability domain of the model; c) **the (Q)SAR result is reliable**: a valid (Q)SAR that is applied to a chemical falling within its applicability domain provides a reliable result; d) **the (Q)SAR model is relevant for the regulatory purpose**: the predicted endpoint can be used directly or following an extrapolation, possibly in combination with other information, for a particular regulatory purpose.

A (Q)SAR prediction (model result) may be considered adequate if it is reliable and relevant, and depending on the totality of information available in a weight-of-evidence assessment (see Section 4 of the QPRF).

1. Substance

This section is aimed at defining the substance for which the (Q)SAR prediction is made.

1.1 **CAS number**: *Report the CAS number.*
1.2 **EC number**: *Report the EC number.*
1.3 **Chemical name**: *Report the chemical names (IUPAC and CAS names).*
1.4 **Structural formula**: *Report the structural formula.*
1.5 **Structure codes**: *Report available structural information for the substance, including the structure code used to run the model. If you used a SMILES or InChI code, report the code in the corresponding field below. If you have used any another format (e.g. mol file), please include the corresponding structural representation as supporting information.*
   a. **SMILES**: *Report the SMILES of the substance (indicate if this is the one used for the model prediction).*
   b. **InChI**: *Report the InChI code of the substance (indicate if this is the one used for the model prediction).*
   c. **Other structural representation**: *Indicate if another structural representation was used to generate the prediction. Indicate whether this information is included as supporting information. Example: "mol file used and included in the supporting information".*
   d. **Stereochemical features**: *Indicate whether the substance is a stereo-isomer and consequently may have properties that depend on the orientation of its*

Quantitative Structure Activity Relationships – QSAR

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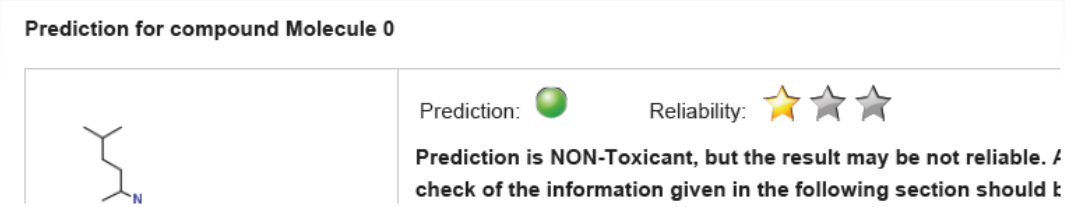
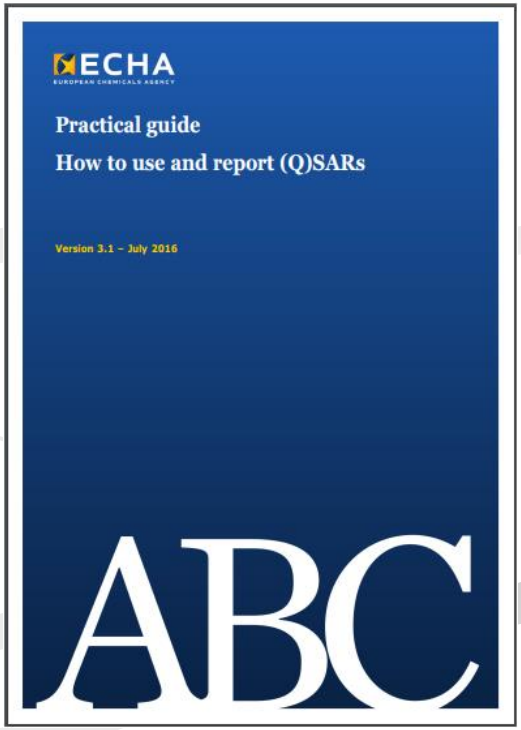
Tips

- If the model doesn't give good results, then don't use it!



- Include the QMRF and QPRF with your submission as justification.
- Take a look at any available Guidance
- Some regions don't like QSAR (e.g China, Australia for some endpoints)



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Waivers

Don't underestimate the use of data waivers!

All schemes have some allowance for waiver of endpoints.

These are usually dependent on other endpoints, particularly phys-chem.

COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
7.5. Vapour pressure	7.5. The study does not need to be conducted if the melting point is above 300°C. If the melting point is between 200°C and 300°C, a limit value based on measurement or a recognised calculation method is sufficient.
7.6. Surface tension	7.6. The study need only be conducted if: – based on structure, surface activity is expected or can be predicted; or – surface activity is a desired property of the material. If the water solubility is below 1 mg/l at 20°C the test does not need to be conducted.
7.7. Water solubility	7.7. The study does not need to be conducted if: – the substance is hydrolytically unstable at pH 4, 7 and 9 (half-life less than 12 hours); or – the substance is readily oxidisable in water. If the substance appears "insoluble" in water, a limit test up to the detection limit of the analytical method shall be performed.
7.8. Partition coefficient n-octanol/water	7.8. The study does not need to be conducted if the substance is inorganic. If the test cannot be

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Waivers

Tips

- **Check region specific waiver criteria; a lot of these are very similar across the schemes.**
- **Check and see if you need to pay for waivers (e.g Australia may charge as data variation); in many cases this is still cheaper than the test itself.**
- **Test smart. For example:**
  Melting Point results can waive boiling point and vapour pressure.
  Water solubility results can waive surface tension, hydrolysis etc.

AND FINALLY….

Most Authorities have Pre-Notification Consultation facilities available.

So use it!!

Check and see in advance if your data strategy is likely to be accepted.

Most Authorities are very helpful in this respect.

In all cases, ensure that your data set is appropriate. You don't want rejection when sales are reliant on approval.

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THANKS FOR LISTENING.