

Possibilities for Research Related to REACH

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1 Summary

REACH (Registration, Evaluation and Authorisation of Chemicals) is an acronym for the new European chemical legislation proposed by the European Commission. It contains the EU regulation for the registration, assessment and restriction of chemicals, and establishment of the European Chemicals Agency (EChA) in Helsinki, Finland. The objective of REACH is to simultaneously protect human health and the environment, maintain the competitiveness of the EU chemical industry, and enhance the innovative ability inside the EU. The REACH regulation is expected to enter into force in 2007.

REACH is a driving force for innovation. New business opportunities are currently being valued all around Europe and companies providing REACH related services are developing innovative new concepts for future business. Some business, such as testing of chemicals, preparation of registration dossiers and exposure scenarios, and development of REACH data systems, are already relatively well defined. Others, like development of *in vitro* or *in silico* alternative testing methods, or new products and processes, may need much more innovative research work before they can be commercialised. The purpose of this discussion paper is to highlight those possibilities for research that are related to REACH and, if successful, can eventually form a basis for future business activity.

Nowadays, a wide variety of existing data needs to be collected and used for risk assessment. And REACH requires physico-chemical, toxicological and ecotoxicological information of substances and their use for the estimation of risk. Many of the testing methods authorised by, for example, the OECD Test Guidelines, are scientifically valid and the results are accurate. But some physico-chemical parameters, such as the n-octanol/water partition coefficients, may need further research due to the data deviations. There is an undisputable trend in the development of alternative methods for replacing several standard animal tests used for the measurement of toxicological endpoints, and the greatest expectations lie on the development of *in vitro* and *in silico* testing methods. Environmental hazard classification in REACH requires the assessment of aquatic toxicity, degradation and bioaccumulation of substances. In order to develop new innovative molecules and processes, industry may also need fast screening tests for chemicals.

Chemicals, through the different stages from their production to their handling, and transport and use, pose a real threat to human health and the environment. To deal with the danger, identifying and assessing the possible hazards of chemicals is required. A hazard assessment is typically carried out in order to consider all the possible effects of concern of the substances being evaluated, and the chemicals are then classified and labelled according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) in order to give a clear and simple description of the associated possible effects to the end users. Hazard identification and assessment is the first step toward a complete risk assessment of a chemical.

If the chemical is classified as dangerous after evaluating the health, environmental and physico-chemical hazards, and possible persistent, bio-accumulative and toxic (PBT) or very persistent and very bio-accumulative (vPvB) properties of the substance, the conditions in which the chemical can be safely used has to be defined. This is performed in the exposure assessment step. Risk characterisation considers both the chemical hazard and exposure to the chemical. To show that risks can be adequately controlled, the manufacturer or importer should develop exposure scenarios as part of the exposure estimation. An exposure scenario (ES) gives realistic conditions under which the substance is manufactured or used (identified uses). It prescribes appropriate or suitable risk management measures (RMMs) that shall be in place during manufacture or use of a substance, and will cover the entire life cycle of the substance. The ES is needed for risk management at the various



life cycle stages to ensure safe handling and adequate control of risk related to human health (workers and consumers) and the environment. Preliminary technical guidance for preparation of, for example, the ES, is provided within the REACH implementation projects (RIPs). However, a lot of expert work is still needed to develop practical tools for the risk evaluation.

VTT has excellent facilities and expertise for developing new innovative tests, methods, and processes related to REACH. VTT especially has expertise to develop methods for the calculation and measurement of physico-chemical properties, such as n-octanol/water partition coefficient data. Thermodynamic multicomponent calculation methods (e.g. ChemSheet) have been proven to provide accurate answers in several industrial cases. VTT has extensive experience in the development of both aquatic and solid state biodegradability tests. In addition, our expertise also concerns the simulation of biodegradability of organic pollutants in different environmental conditions. Methods for monitoring the degradability of organic pollutants in the environment and monitoring tools based on molecular biology to detect catabolic genes and microbes involved in the degradation processes have been developed. Risk assessment involves studies concerning the environmental toxicity of chemicals and VTT also has a broad range of expertise in environmental toxicity studies. In addition, VTT has research ongoing to perform physico-chemical analysis of chemicals, modelling of the fate and behaviour of chemicals in the environment, e.g. absorption, bioavailability, biodegradability and environmental toxicity. Because the environmental effects of chemicals cannot be confirmed by standard biodegradability and ecotoxicity tests, there is a need for further research to develop simulation tests and to study the behaviour of chemicals in nature.

An emerging toxicological research field is that of toxicogenomics, which involves the use of 'omics' technologies such as genomic scale mRNA expression (transcriptomics), cell and tissue-wide protein expression (proteomics), and metabolite profiling (metabolomics) and bioinformatics, to analyse the data. VTT has extensive expertise in several areas related to *in vitro* toxicology; e.g. the development of *in vitro* tests based on cell and tissue cultures, and the development of 'omics' techniques for studying gene expression in human and environmental applications. System biology, combined with environmental exposure and ecotoxicological studies, could be applied as dose response studies in the future.

VTT information services can provide the information needed for building up the ES. We can offer, for example, publicly available information sources to identify uses, search for available information on the properties of the substances, information concerning the exposure, and also information on the available RMMs. Extensive in-house information on chemical uses around the world has already been collected. VTT also has expertise on developing different kinds of information systems, which can be used to facilitate communication between the manufacturers/importers and the downstream users (DUs) – while taking into consideration any relevant confidential business information (CBI). Research work has been performed on determinants of exposure such as the identification of factors affecting styrene exposure and the factors affecting the substance becoming airborne. VTT has participated in the development of video exposure monitoring tools (e.g. PIMEX), and been active in their effective utilisation in occupational hygiene work. VTT's Kemi-Arvi 3.1 is designed to help companies, especially small and medium-sized enterprises (SMEs), assess whether their chemical risks are adequately controlled – based on the properties of the substance, the route of exposure, the handling of chemicals, the technical control measures or personal protective equipment (PPE) implemented, and the organisational measures in use. The tool is question-based and easy to use, and covers both continuous occupational exposure, as well as accidental exposure. The Kemi-Arvi tool may also be used in ES building after some development. VTT has a long tradition in measuring both occupational and non-occupational exposure to chemicals, as well as identifying their sources and source strengths.

In several industrial projects VTT has also gathered diverse experience in the assessment of environmental risks of contaminated sites, landfill disposal of waste, and the utilisation of industrial waste in earthworks, as well as investigating the risk assessment of nuclear waste disposal alternatives. The most important expertise areas include the investigation and assessment of toxic chemicals emissions leaching from various materials (e.g. soil, by-products and wastes, construction products, ores and minerals) using leaching tests and leaching models, transport models, a combination of leaching data and transport modelling, the estimation of emissions to air, ecotoxicological tests, the management of risk assessment projects, environmental ESs, and life-cycle assessment of processes and products.

VTT has facilities and expertise for developing RMMs and detecting their performance for both environmental and occupational risks. The expertise covers, for example, PPE, safety, health and environment in small process plants, and the accidental releases of chemicals. Studies concerning the performance of technical control measures include modelling the performance of local ventilation systems, the measurement of the performance, and identification of the determinants of the performance. Also, control measures to various industrial applications (exposure scenarios) have been developed and their efficiency evaluated under actual workplace conditions. The performance of various air filters, the determinants of the efficiency, as well as development of novel air filtration systems are also key research topics at VTT.

VTT has a wide range of knowledge on most of the issues associated to performing a socio-economic analysis (SEA). Expertise can also be provided in additional health and environmental aspects of alternatives, economic feasibility studies, technical evaluations, and impact analyses on both social and industrial interdependencies, as well as in the knowledge of the entire stakeholder networks; especially concerning their formation and functionality under different constraints. There is a possibility to provide new wider service concepts by unifying several different expertises into a single analysis. These service concepts may also include expertise outside VTT whenever deemed necessary.

VTT has participated in the design of safer chemicals and processes, the optimisation of the use of hazardous chemicals, and also new technology development. Some examples covering the development of safer products and processes include new synthetic techniques that combine approaches of biology, physics and computational methods, new catalysts and reaction systems, chemistry for the use of alternative raw materials, synthesis tools to create multi-functional materials, and chemistry in alternative reaction media.

The fundamental task of the REACH system is to collect the best available information regarding hazardous chemicals, and then control their use in order to minimise the risks on humans and the environment. It is our responsibility to the next generations to develop new tools, techniques and methods to ensure that this goal is achieved.

2 Introduction to REACH

2.1 General

On October 29, 2003, the European Commission issued a proposal for the new chemical legislation (COM(2003)644) known as REACH (Registration, Evaluation and Authorisation of Chemicals). It contains the EU regulation for the registration, assessment and restriction of chemicals, and the establishment of European Chemicals Agency (EChA). The objective of REACH is to simultaneously protect human health and the environment, maintain the competitiveness of the EU chemical industry, and enhance the innovative ability within the EU.

There is a general obligation to register substances on their own, and substances in articles or in products. However, the essential administrative procedure is directed at substances and not articles or products. Substances are defined as chemical elements or their compounds, such as they occur in nature or are produced in processing. The REACH proposal covers the use, production, importing and launching of substances and chemicals. To promote innovation, substances used for product and process-oriented research and development are exempted from the general obligation for registration. This exemption shall be valid for a certain period of time. The following substances are exempt:

- Radioactive substances are exempted because they are addressed by other legislation,
- Substances in plant protection and biocidal products,
- Non-isolated intermediates and transported isolated intermediates,
- Side products formed in chemical reactions or processing in general,
- Custom controlled substances, that are kept in a free zone or temporary storehouse awaiting transit,
- Pharmaceutically active substances,
- Polymers.

The REACH proposal (and its annexes) embodies several scope restrictions related to registration, evaluation and authorisation. The general principle is that substances addressed by other legislation are exempted (e.g. biocides, pharmaceuticals, plant protection).

2.2 Description of REACH

The most important objective of the REACH proposal is the safe use of chemicals. This objective will be achieved by controlling the risks related to the use of chemicals, as the risks arise from the hazardous chemical properties and exposure to the chemicals.

To determine the risks, the properties of chemicals, together with the anticipated exposure, are estimated in real operating situations. Information related to the exposure and the way of using the chemicals will be provided by the user, and this information will be passed both up and down the supply chain and between all actors in supply chain. The tool primarily used for such information transfer is the safety data sheet (SDS).

REACH proposes that manufacturers and importers of chemicals evaluate the risks of using the chemicals and will implement any necessary measure to control the observed risks. The responsibility of the safe use of chemicals on the market will be transferred from the authorities to industry.



REACH consists of the following elements:

- Registration requires industry to obtain relevant information on their substances, and to use that data to manage them safely.
- Evaluation provides confidence that industry is meeting its obligations, prevents unnecessary testing and identifies substances that can be harmful for health and the environment.
- Risks associated with uses of substances with properties of very high concern will be reviewed and, if they are adequately controlled, or if the socio-economic benefits outweigh the risks and there are no suitable alternative substitute substances or technologies, then the uses will be granted an authorisation.
- The restriction procedure provides a safety net to manage risks that have not been adequately addressed by another part of the REACH system.

Registration

Registration of substances is the primary item in the REACH system. There is a general obligation to register substances manufactured or imported in quantities starting at 1 tonne/a. All the basic substance registration information is collected in a centralised database. Registration information will be utilised in all other REACH administrative processes.

The registration is carried out by the manufacturer, the EU importer or their coalition. Failure to register means that the substance cannot be manufactured or imported. The EChA will receive the registration documents and will maintain a database containing all the registration information.

Registration requires the submission of a technical dossier containing all the relevant information on the substance and information on RMMs. Starting at 10 tonnes/a, a chemical safety report documenting the choice of RMMs is also required. The registration obliges manufacturers and importers to obtain knowledge on the substance they manufacture or import, and to use this knowledge to ensure that the risks are appropriately managed. The technical dossier requires information on the properties of the substance and their safe use. Manufacturers and importers shall address the risks of any use identified to them by their downstream users (DUs). A DU has the right not to identify a use, in which case the responsibility for carrying out a chemical safety assessment (CSA) will be shifted to them.

It is proposed that the tonnage use of a chemical gives an indication of its exposure, and therefore the information requirement is modulated by tonnage. The least information is required in the case where a substance is manufactured or imported in amounts of less than 10 tonnes/a. Although a safety assessment is then not required, physico-chemical properties, toxicology and eco-toxicology information is still needed.

A number of rules regarding data sharing are set out in order to reduce the burden of the costs on industry and the need for repetitive testing on vertebrate animals. Relevant data are to be shared provided that parties have agreed on the related payment.

For the registration of substances in articles, a special regime applies. There are millions of articles placed on the EU market that contain substances, which potentially may cause harm to human health and the environment. Certain substances in articles need to be registered. This is required when the substance in question has hazardous properties and is expected to be released from the article. For substances that are released only incidentally from articles, a simple notification is required, on the basis of which the EChA may request a registration.



Evaluation

The aim of the evaluation procedure is to check that industry obeys the requirements of REACH, and also that unnecessary animal testing is avoided. There are two types of evaluation: dossier evaluation and substance evaluation. Both evaluations may require further information on a substance.

An important aim of the dossier evaluation is to examine proposals for animal testing in order to check the quality before a test is performed and to prevent overlapping animal testing. The REACH system encourages data sharing and recommends that manufacturers and importers apply alternative methods instead of animal testing for the acquisition of information. Obviously, dossier evaluation is needed to check compliance of the registration dossier with the requirements of the registration title.

If the substance is expected to pose a risk for human health or the environment, the Member State's competent authority can stipulate that the industry provides further information on a substance for evaluation. The EChA will develop guidance on the prioritisation of the substance for evaluation and the Member States then prepare plans for the substance they prefer to evaluate. A decision for requiring further information must be accepted by the other Member States. There is a procedure for resolving disagreements over which Member State should evaluate any particular substance. In case the Member States disagree, the decision is made by the Commission.

The evaluation may lead authorities to the conclusion that the action should be taken under the restriction or authorisation procedures in REACH, or that information should be passed to other authorities responsible for the relevant legislation.

Authorisation

REACH contains an authorisation system for uses and for the placing on the market of selected substances that possess a significant risk for human health or the environment. Authorisation ensures that the risks are assessed, weighted, and then finally decided upon by the Community prior to the actual use.

Authorisation covers selected substances such as:

- CMRs (substances being carcinogenic, mutagenic and toxic for reproduction category 1 & 2),
- PBTs (substances that are persistent, bio-accumulative and toxic),
- vPvBs (substances that are very persistent and bio-accumulative),
- Substances that are known to possess severe and irreversible effects on human health and the environment, such as substances that act as endocrine disrupters.

The burden of proof is placed on the applicant; the applicant needs to demonstrate that the risk from the use is adequately controlled or that the socio-economic benefits outweigh the risks. DUs can use the substance according to the authorisation as long as they receive the substance from a company for whom an authorisation has been granted and they keep within the conditions of that authorisation. The DUs that are authorised to use a selected substance need to inform the EChA of their use so that the authorities are fully aware of how and where substances of very high concern are being used.

Restrictions

The restriction provisions enable RMMs to be introduced across the Community where there is shown to be a necessity. The restriction provisions set a safety net to control risks that are not covered sufficiently in other items of the REACH system. Proposals for restrictions may consist of



conditions for the manufacture, uses and placing on the market of a substance, or of the prohibition of these activities if necessary. The Member States or the Commission shall prepare the proposals for restrictions in the form of structured dossiers.

2.3 European Chemicals Agency (EChA)

The REACH proposal contains the establishment of the European Chemicals Agency. The EChA will be located in Helsinki, Finland. The EChA will manage the technical, scientific and administrative aspects of the REACH system. The main mission of the EChA is to guarantee the consistency of decision making at the Community level.

The EChA is an independent European office. It will:

- manage the registration process,
- maintain the registration database ,
- guarantee the consistency of the evaluation process,
- prepare standards to guide the Member States in the process of selecting the substances for evaluation,
- play a key role in decision making related to the evaluations of testing proposals and compliance of the information with the requirements of REACH,
- provide opinions and recommendations in the authorisation and restriction procedures.

The fundamental goal of the REACH regulation is to ensure the safe use of chemicals. The safe use of chemicals calls for the gathering of information on chemical properties and their usage, and this information needs also to be distributed to the end-user level. The EChA will play a key role in the chemical hazard communication, as most of the non-confidential registration information will be available free of charge for the end users via the EChA's website.

2.4 Approval of REACH regulation

The European Parliament's first reading was finalised on November 17, 2005, and the Council reached a political agreement on December 13, 2005. The final adoption of the proposal is expected to take place in 2006 and the REACH regulation is expected to enter into force in 2007, twenty days after being published in the Official Journal of the European Union. The regulation will be legally binding in all EU member states immediately after entering into force (with the exceptions described in Article 137, "Entry into force and application"), but there will be a transition period of up to 18 months during which the EChA will not yet be fully operational, and during this period, the Commission will fulfil the relevant functions. After this transition period, the pre-registration of the existing "phase-in" chemicals, as well as the registration of the new "non-phase-in" chemicals, starts.

3 Testing methods

The current legally binding EU standardised testing methods to determine the hazardous properties of chemicals are given in Annex V of Directive 67/548/EEC on the Classification, Packaging and Labelling of Dangerous Substances. Many of these methods are adaptations of internationally recognised standards (ISO, UN, OECD). In particular, the development of Annex V testing methods is closely linked and co-ordinated with the OECD Test Guidelines programme¹.

The European Chemicals Bureau (ECB) is responsible for the scientific and technical aspects of developing new testing methods², revising the existing methods and organising transfer of internationally accepted standards (e.g. OECD Test Guidelines) into Annex V. The ECB works in close co-operation with the European Centre for Validation of Alternative Methods (ECVAM) and the Group of National Coordinators for Testing Methods, a group of experts from the Member States representing the Competent Authorities of the States, on all method development issues. The Commission (Environment DG), upon advice of the ECB, proposes to the Member States the methods which should be introduced into Annex V. This is done by a formal procedure called Adaptation to Technical Progress (ATP) of the Directive 67/548/EEC.

The most recent ATP (the 29th) took place in April 2004 and involved the inclusion or revision of 13 methods in Annex V. The next ATP, whose date has not yet been scheduled, might include 8 new or revised methods, as seen in Table 1. Some other methods might also someday be added to Annex V (Table 2).

Table 1. Testing methods under the ATP revision procedure.

Name	Description
New A.xx	Length weighted geometric mean diameter of fibres
Updated B.40	<i>In vitro</i> skin corrosion TER
Updated B.40 bis	<i>In vitro</i> skin corrosion HSM
Updated B.41	<i>In vitro</i> photo-toxicity 3T3 NRU test
New B.44	<i>In vivo</i> skin absorption
New B.45	<i>In vitro</i> skin absorption
Updated C.2	Daphnia sp. acute immobilisation test
Updated C.7	Hydrolysis as a function of pH

Table 2. Potential testing methods for ATP revision.

Name	Description
Updated A.4	Vapour pressure
Updated A.8 bis	Partition coefficient (n-octanol/water) using a HPLC method
New B.xx	Acute oral toxicity. Up and down method
Updated C.2	Daphnia sp. acute immobilisation test
Updated C.7	Hydrolysis as a function of pH
New C.xx	Simulation test: Aerobic sewage sludge plant
New C.xx	Biodegradation in surface waters
New C.xx	Sediment-water chironomid toxicity test using spiked sediment
New C.xx	Sediment-water chironomid toxicity test using spiked water
New C.xx	Enchytraeid reproduction test
New C.xx	Earthworm reproduction test
New C.xx	Leaching in soil columns



3.1 Data requirements for Safety Data Sheet (SDS) and Chemical Safety Report (CSR)

A Chemical Safety Report (CSR) is a document that provides industry a tool for demonstrating that it can use chemicals safely. Manufacturers and importers are required to prepare a CSR for substances in volumes at or above 10 tonnes/a. A Safety Data Sheet (SDS) consists of summaries of information on the properties of substances and the safe means of using them. They also provide established means of transmitting safety information down the supply chain.

A SDS is required for all substances produced or imported at or above 1 tonne/a. The data requirements of the SDS and CSR are similar, and the amount of data required increases with the volume of the substance production or import according to Annexes V-VIII of the proposed REACH regulation. The test method requirements will be direct implementations of the current 67/548/EEC Annex V methods and their further refinements. Annex V currently contains 92 testing methods and about 40 testing methods are under development or revision. Annex V is contains 3 parts: A) physico-chemical properties, B) effects on human health, and C) environmental effects. Out of the current 92 test methods, 20 methods are described in Part A, 43 in Part B, and 29 in Part C.

3.1.1 Physico-chemical testing

The physico-chemical parameters required for a SDS and CSR, and their current testing methods, are briefly reviewed in the following subchapters. The emphasis is on possible refinements of the existing techniques and potential new methods, a more detailed description of the current methods can be found in Directives 92/69/EEC³, 98/73/EC⁴ and 2004/73/EC⁵.

The standard information requirements of REACH include the following physico-chemical properties of substances: melting/freezing point, boiling point, relative density, vapour pressure, surface tension, water solubility, water/n-octanol partition coefficient, flash point, flammability, explosive properties, self-ignition temperature, oxidising properties, and granulometry. Information about the stability of a substance in organic solvents and relevant degradation products, and the dissociation constant and viscosity, may also be required for chemicals with a production volume of 100 tonnes/a or more. Additionally, any other information considered appropriate for the risk assessment is also required (i.e. pH, Henry's law constant, etc.). REACH related physico-chemical parameters are listed in Table 3.

The variability of available physico-chemical data has been studied in a recent survey⁶ covering 8 data sources and 755 chemicals which appeared in at least 4 sources and belonged to 7 environmentally important subprojects. Molecular weight, melting point, boiling point, vapour pressure, water solubility, Henry's law constant, octanol/water partition coefficient and diffusion coefficients in air and water, were the properties chosen for the study. The results indicated that there is considerable variation in the data sets for octanol/water partition coefficient, vapour pressure, water solubility, and the Henry's law constant, when compared to the measurements for molecular weight, melting point, boiling point or diffusion coefficient in water.

Table 3. Important physico-chemical parameters related to REACH.

Physico-chemical parameter	Methods applied 92/69/EEC	Estimated data accuracy	Activities	Research needs
Melting/freezing temperature	Melting point Capillary methods Hot stages methods Freezing point Thermal analysis (DTA, DSC) Pour point	Good (± 0.5 K)	No major activities	No significant research needs
Boiling point	Measurement of boiling temperature (e.g. ebulliometer, distillation, photocell) Thermal analysis (DTA, DSC)	Good (± 0.3 K – ± 2 K)	No major activities	No significant research needs
Relative density	Buoyancy methods Pycnometer methods Air comparison pycnometer Oscillating densitometer	Good	No major activities	Measurements are simple and accurate. There are no significant research needs
Vapour pressure	Dynamic method Static method Isoteniscope Effusion methods Gas saturation method Spinning rotor		Knudsen cell method and isothermal gravimetry were just adopted by OECD	No single procedure is applicable to the entire range of vapour pressures from less than 10^{-10} to 10^5 Pa and this highlights research needs
Surface tension	Plate method Stirrup method Ring method OECD harmonised ring method	Good precision	No major activities	No significant research needs
Water solubility	Column elution method ($< 10^{-2}$ g/l) Flask method ($> 10^{-2}$ g/l)	Good precision	No major activities	No significant needs for pure water measurements. In nature, water contains salts, organics, etc. that affect the solubility
Partition coefficient (n-octanol/water)	Shake-flask method HPLC method	Relatively large data deviations	Active research	Presence of impurities, emulsions, dissociation and ionisation create challenges and better methods and models are needed
Flash point	Equilibrium method(Open cup method) Non-equilibrium method (closed cup methods) Abel-Pensky apparatus Tag apparatus Pensky-Martens apparatus	Deviations, but data may be accurate enough for risk assessment purposes	Some activity related to development of calculation methods	No pressing research needs. Methods to calculate the flash point could prove to be useful.
Flammability	A10. Flammability (solids) A11. Flammability (Gases) A12. Flammability (Contact with water)	Qualitative screening test	No major activities	No significant research needs
Explosive properties	A14. Explosive properties - Tests for thermal sensitivity, sensitivity with respect to shock and with respect to friction	Qualitative screening test	No major activities	No significant research needs
Auto-ignition temperature	A15. Auto-ignition temperature (Liquids & gases) A16. Relative self-ignition temperature (Solids)	Preliminary screening – Data for comparison purposes only	No major activities	No significant research needs
Oxidation properties	A17. Oxidising properties (Solids) A21. Oxidising properties (Liquids) – adopted in Dir. 73/404/EEC	Preliminary screening – Data for comparison purposes only	No major activities	No significant research needs
Granulometry	Cascade impaction, laser scattering / diffraction and the rotating drum method	Good accuracy	A draft of the testing methods prepared	Active research

Some of the properties mentioned above are easier to measure than others, so from the research point of view, the properties which are difficult to measure with the current methods or have problems with data reliability are the more interesting. Test methods for explosive and oxidising properties of materials, and the flammability test, are designed to give only qualitative information on the substance, or the information obtained from the tests is given in physically less meaningful terms that usually also depend on the testing equipment used, and these methods are considered less interesting from the research point of view.

There is also already a wealth of accurate test methods for the measurement of boiling and melting points, relative density and surface tension, and we could not find any ongoing research that focuses on the possible refinements of these methods. There is, however, some ongoing research focusing on vapour pressure⁷, granulometry^{8,9} and octanol/water partition coefficient^{10,11} measurements.

It should also be mentioned that for every physico-chemical property, the assessment shall, in addition to the tests, entail an evaluation of the likelihood (risk) that an adverse effect will be caused by the chemical under the reasonably foreseeable conditions of use in the workplace, or by consumers. The safety assessment, to be presented in the Chemical Safety Report, shall document that the risks are adequately controlled.

The assessment of the potential effects arising from the capacity of hazardous chemical agents to cause accidents (i.e. in particular: fires, explosions or other hazardous chemical reactions) covers:

- hazards resulting from the physico-chemical nature of the chemical agents,
- risk factors identified in their storage, transport and use, and
- estimated consequences in the event of occurrence.

An example of a simplified assessment, including a questionnaire for the DUs on their use conditions, has been developed by DG Employment in the context of Directive 98/24/EC.

Partition coefficient (n-octanol/water)

The most important physical property affecting the biological activity of substances is their lipophilicity. Lipophilicity is usually expressed in terms of the n-octanol/water partition coefficient $K_{o/w}$, the logarithmic ratio of concentrations of substance i in the octanol and water phases, respectively. The partition coefficient is widely used in the development of environmental fate models, in the estimation of bio-accumulation in animals and plants, and in the prediction of toxicity and drug absorption¹². Although partition coefficients have been measured in many different solvent-water systems, octanol/water is the most widely accepted reference system because of its correlation of physico-chemical properties with biomembranes¹³. Moreover, several quantitative structure-activity relationships (QSARs) use $\log K_{o/w}$ for predicting such compound properties as permeability through membranes, binding at receptor sites, bacterial spore germination, inhibitory activity, amongst others¹⁴.

There are currently two methods described in the 92/69/EEC Directive for octanol/water partition coefficient measurements: the shake flask method and high performance liquid chromatography (HPLC). The former is applicable when the $\log K_{o/w}$ value falls within the range of -2 to 4 and the latter within the range of 0 to 6. Before carrying out either of the experimental procedures, a preliminary estimate of the partition coefficient should first be obtained.

There are two new methods for octanol/water partition coefficient determination under evaluation in the OECD Test Guidelines programme at present: slow-stirring method¹⁰ and pH-metric method¹¹

for ionisable substances. The slow-stirring method was recently adopted into the OECD testing guidelines. Both of these methods are potential candidates to be later included in the EU standardised testing methods.

The slow-stirring method, first introduced by Brooke *et al.*¹⁵, is a method developed from the shake-flask method, in which the mass transfer between adjacent phases is only enhanced by slowly stirring the solution. In this method, the interface between water and octanol phases is not perturbed and thus the risk for emulsion formation is greatly reduced. The slow stirring method is the method of choice especially for highly hydrophobic compounds, as it was recently demonstrated to provide reliable log $K_{o/w}$ data up to log $K_{o/w}$ of 8.3 in a validation study¹⁶ involving measurements carried out in 15 different laboratories. However, the method is very time-consuming, as it can take several days to reach the equilibrium between the two phases.

The pH-metric method provides a fast and reliable method for octanol/water partition coefficient determination for ionisable and multiprotic compounds having a log $K_{o/w}$ value in the range from -2 to 7. The method consists of two sequential, linked potentiometric titrations. The pK_a value of the substance is first determined in aqueous solution by acid-base titration, followed by addition of the octanol phase into the system and the determination of an apparent p_0K_a value in two phase system by a second titration. The difference in the two pK_a values measured is related to the value of log $K_{o/w}$, thus making it possible to calculate the partition coefficient from the shift of the pK_a value. The pH-metric method has been validated against the traditional shake-flask method¹⁷ and has a good potential in replacing that method as a primary validation method for ionisable molecules. The method has also been studied against the HPLC method¹⁸ with good results, and there is a closely related technique for pH-metric solubility determination¹⁹ that has been tested against shake-flask solubility measurements.

Other methods for octanol/water partition coefficient determination, such as the generator-column method²⁰ and methods based on capillary electrophoresis²¹⁻²³, solid-phase microextraction^{12,24,25}, centrifugal partition chromatography²⁶, cyclic voltametry^{27,28} or flow-injection extraction^{29,30}, have also been studied. In general, these methods are only usable for a relative narrow measurement range of partition constants, or have proven to be either too time consuming, unreliable or technically challenging³¹.

Calculation methods for estimating physico-chemical properties

The current computational methods for the estimation of some physico-chemical properties of chemicals are briefly reviewed here. Measured data is generally always preferred over data generated with theoretical models, but nevertheless there are two physico-chemical properties for which there exists a possibility to use a calculated value (instead of a measured one) are mentioned in the Annex V testing methods: octanol/water partition coefficient and flash point.

Calculation methods are allowed for octanol/water partition coefficient determination in the current EU legislation only in the case when there is a well-justified reason as to why any of the experimental methods cannot be applied. Calculated values of $K_{o/w}$ can still be useful for deciding which of the experimental methods are appropriate, and for selecting the appropriate test conditions. All calculation methods given in 92/69/EEC (Hansch π -method³², Rekker method³³, Hansch-Leo method³⁴) are based on the formal fragmentation of the molecule into suitable substructures for which reliable log $K_{o/w}$ increments are known or can be estimated from existing data. The log $K_{o/w}$ of the whole molecule is then calculated as the sum of its corresponding fragment values, plus the sum of correction terms for intramolecular interactions. Methods based on this approach are known as

group contribution methods, in general. A number of refinements of the group contribution methods, with a variable number of different groups involved and different methods used for the parameter optimisation, have been presented³⁵⁻³⁸. It is relatively complicated and time consuming to take into account all the rules and correction terms involved in these models, but there are several software packages such as CLOGP³⁴, KLOGP³⁹, KOWWIN⁴⁰ (free download of EPISuite package, including KOWWIN, available from the U.S. Environmental Protection Agency website), and XLOGP³⁸, have been developed to simplify the task. Mannhold *et al.*⁴¹ compared 14 different calculation procedures for partition coefficient estimation with a test set of 138 organic compounds and found KOWWIN to be the most reliable method, and Wang *et al.*³⁸ demonstrated later that the reliability of XLOGP is comparable to KOWWIN.

Other approaches to calculate partition coefficients include the use of linear solvation energy relationships⁴²⁻⁴⁴, molecular volume based approaches^{45,46}, the Hartree-Fock equation and Monte Carlo simulations⁴⁷, molecular orbital calculations combined with neural network analysis⁴⁸, and molecular dynamics simulations⁴⁹. Although the current state of the art in molecular dynamics simulations does not yet allow the calculation of the exact partition coefficient values in hydrophobicity scale, such calculations may become viable in the near future, allowing a direct calculation method for partition coefficients (all the other methods are indirect, as they rely on existing partition data or other measured values). The existing calculation methods can be used for partition coefficient estimation with acceptable accuracy³⁸, at least for chemical risks assessment purposes, and there is continuous development in the field of creating better calculation methods. Bearing in mind the variability of existing literature data, as pointed out by Renner⁵⁰, the current experimental methods may be superseded by theoretical calculations in the near future.

Several empirical equations for predicting flash points, starting with simple relationships between the flash point and the normal boiling temperature, and adding more parameters or group specific constants as the models have been further developed, have been presented⁵¹⁻⁵⁹. Some of these equations contain quite peculiar parameters, for example, liquid density is used as a parameter in the equation⁵⁶ presented by Metcalfe *et al.*, but Hshieh⁵⁸ *et al.* have shown that there is no statistical correlation between liquid density and flash points. Other approaches estimating flash points include the use of quantitative structure-property relationship (QSPR) analysis and neural networks^{60,61} and group contribution based methods^{62,63}. Computer programs⁶⁴⁻⁶⁶ for calculating the flash point estimations with group contribution methods are also commercially available. Keeping in mind the quality of current measurement methods^{67,68} and errors in the literature data⁵⁹, any of the correlations presented here should be able to give acceptable estimations for flash points if there is accurate flash point data available for chemically similar compounds, and the model used is able to predict flash point values for those compounds with reasonable precision.

Thermodynamic simulation models, based on the minimisation of the overall Gibbs energy of a multi-phase system, have been developed for different chemical equilibrium systems. The ChemSheet⁶⁹ program is a practical tool for thermodynamic simulation. It combines the flexibility and practicality of spreadsheet operations with rigorous, multi-phase thermodynamic calculations. The application fields include process models in chemistry and metallurgy, ion exchange models, temperature and heat in reactive multi-phase systems, material chemistry, and studies for emission chemistry and environmental problems. ChemSheet can be used to model a wide range of non-ideal systems, such as dilute and concentrated aqueous systems, which makes it an interesting tool for modelling the n-octanol/water partition coefficient.

Static electricity

The proposed REACH regulation states that "For every physico-chemical property, the assessment shall entail an evaluation of the inherent capacity of the substance to cause the effect resulting from the manufacture and identified uses". It is also noted that "As a minimum, the potential effects to human health shall be assessed for the following physico-chemical properties: explosivity, flammability and oxidising potential. However, several studies have shown that the accumulation of static electricity on chemicals raises the potential risk for explosion. Therefore, the electrostatic properties of the substances should also be considered in the physico-chemical hazard assessment.

Electrostatics has not been addressed in REACH, but it we believe that there is a need for research also within the context of REACH in spite of the fact that many aspects of static electricity are covered by the ATEX Directives.

VTT has several experts on electrostatic hazards and the facilities for testing electrostatic phenomena.

3.1.2 Toxicological testing

The following toxic endpoints in chemical toxicity assessment need to be studied: acute and chronic toxicity, eye irritation, skin corrosion/irritation, skin sensitisation, mutagenicity and genotoxicity, repeated-dose toxicity, carcinogenicity, reproduction toxicity, aquatic toxicity, and degradation.

In exposure studies, both testing methods described in Annex V of Directive 67/548/EEC on the Classification, Packaging and Labelling of Dangerous Substances and non-testing methods like (Q)SARs are employed. The endpoint results of the testing protocols included in the approved testing methods are used as a basis for classification and labelling, risk characterisation and risk assessment studies.

The endpoint in risk characterisation for human health can be, for example, Margin Of Safety (MOS), that is, No Observed Adverse Effect Level (NOAEL) divided by exposure. On the other hand, risk in the environment is presented differently. For example, PEC (Predicted Environmental Concentration) /PNEC (Predicted No-Effect Concentration) is one of the parameters that describe the research need for the effects of the chemical in the environment. Integrated testing strategies use endpoint information from existing data, *in vitro* studies, ESs, (Q)SARs and based on all this combined information, a decision about the need for further testing is made (Table 4).

Most human toxicity tests are based on the use of test animals especially rodents such as rats, mice and guinea pigs, which are exposed to chemicals, and toxicological endpoints measured. The tests used to study ecotoxicological impacts are applying different trophic-level organisms such as the water flea, algae, the earthworm, and fish. A bacterial growth inhibition test can be considered to be especially important for evaluating the adverse effect of chemicals on sewage treatment plant processes.

Toxicity for humans is still mainly based on the use of *in vivo* tests and there are only a few *in vitro* tests that have been accepted and validated for regulatory purposes. The problema with toxicity testing may occur in the form of specificity of the test animal's response to chemicals, which does not correlate to the response for humans. All the existing information concerning the chemicals and their human exposure mechanisms and intrinsic properties from the scientific literature, is utilised for human risk assessment. Historical human data such as epidemiological studies concerning

carcinogenicity, reproductive toxicity various forms of systemic toxicity and skin sensitisation is also considered⁷⁰. In addition, the ecological factors such as environmental toxicity, degradation of chemicals in the environment, bioaccumulation and fate of chemicals also have to be studied.

Table 4. Some of the main endpoints and abbreviations that are relevant within REACH.

Endpoint	Description	Additional info or use
EC50	Effective concentration 50%	Concentration that produces 50% of the maximum possible response.
LC50	Lethal concentration 50%	Concentration that kills 50% of the test organisms in a given time
LOAEL	Lowest Observed Adverse Effect Level	
LOEC	Lowest Observed Effect Concentration	
NOAEL	No Observed Adverse Effect Level	
NOEC	No Observed Effect Concentration	
DNEL	Derived No-Effect Level	DNEL/PNEC
PNEC	Predicted No-Effect Concentration	PNECs are derived from acute and chronic toxicity test results like EC50, NOEC, etc. DNEL/PNEC, PEC/PNEC
PEC	Predicted Environmental Concentration	PEC/PNEC
PBT	Persistent bio-accumulative toxic	PBT/vPvB assessment
vPvB	very Persistent very Bio-accumulative	PBT/vPvB assessment

In the SDS, a comprehensive description of the toxicological effects includes information about the exposure routes (inhalation, ingestion, skin and eye contact), symptoms related to toxicological characteristics, the effect of short-term and long-term exposure, acute toxicity are considered, etc.

3.1.3 Ecotoxicological testing

Environmental hazard classification of substances is based on bioaccumulation and persistence of chemicals to persistent bio-accumulative and toxic compounds (PBT) and very persistent and very bio-accumulative substances (vPvB). The criteria for classification are based on degradability and toxicity of substances.

Environmental hazard classification in REACH requires assessment of the aquatic toxicity, and degradation and bioaccumulation of substances. All the existing data is collected and used for the risk assessment. The development of guidelines for testing biodegradability is ongoing in RIP projects as well as for the development of the Globally Harmonised System of Classification and Labelling of Chemicals (GHS)⁷¹.

In addition to the estimation of biodegradability and toxicity of chemicals, the impacts and behaviour of degradation products on different trophic-level organisms are key factors when evaluating the risk of chemicals for the environment. Information about the abiotic and biotic degradation of chemicals is required in the "Base set" for the Technical dossier. Standard biodegradation tests are grouped into ready biodegradability tests, inherent biodegradability tests and simulation tests. This classification will categorise the chemicals as fast biodegradable and to tentatively bio-accumulative compounds which may be persistent in the environment. The chemicals which pass the ready biodegradability tests are considered to be easily biodegradable in the environment. Six methods for screening ready

biodegradability of chemicals in aerobic aqueous media are listed in Annex V of Directive 67/548/EEC, Part C. These methods are based on measuring CO₂ production or O₂ consumption. If the substance is not readily biodegradable, a need for testing the hydrolysis as a function of pH should be considered. Other methods mentioned in the Annex V Part C are the degradation measured as Biological Oxygen Demand (BOD) or Chemical Oxygen Demand (COD), Zahn-Wellens test evaluating biodegradation, activated sludge simulation and respiration inhibition tests, and modified SCAS test. Methods for measuring transformation of chemicals in soil and aquatic sediments are listed in Annex V of Directive 67/548/EEC.

If the chemical is inherently biodegradable, there is need for specific species of micro-organisms, e.g. enriched inoculum, to degrade the chemical. When testing biodegradability in laboratory test systems, the potential of a chemical to be biodegraded in the environment can be predicted. However, inherently biodegradable chemicals may accumulate or bioaccumulate in the environment and therefore chemicals classified in inherently biodegradable or non-biodegradable are of high concern. In testing situations, the amount of chemical is generally higher than in real life conditions and the tests are generally performed at optimised conditions. Therefore, the results generated in the laboratory may not directly comparable to the biodegradation in the environment. Simulation tests have been developed to simulate the effect of different environmental conditions to degradation.

When the chemical is considered to be biodegradable, it is expected to pass (degrade) the ready biodegradability tests during a certain time frame. As these tests are performed in optimised conditions, the results are not directly comparable to the environmental conditions; several variables such as low temperature, lack of nutrients, oxygen, etc. restrict biodegradation processes in the natural environment. Especially in the Nordic climatic conditions, the warm season is short and the time for degradation is therefore also much shorter than in Central- and Southern-Europe. Estimating the biodegradation of chemicals in nature is difficult and varies widely depending on the local and global conditions.

Several aspects are still difficult to include into chemical testing. For example, if the concentration of a substance in the environment is much smaller than the one tested in a laboratory experiment, it often reduces the biodegradation rate. Often, chemicals also are present as mixtures in the environment, and testing typically considers the application of only a single substance.

The physico-chemical properties also affect the distribution and fate of chemicals. Absorption on soil particles and bioavailability affect the biodegradability. All these different environmental properties, in addition to the climatic conditions, make it difficult to estimate the behaviour of chemicals in the environment.

VTT has extensive experience in the development of biodegradability tests – of both aquatic⁷²⁻⁷⁴ and solid state tests⁷⁵. In addition, our expertise covers also the simulation of biodegradability of organic pollutants in different environmental conditions^{76,77}. Methods for monitoring the degradability of organic pollutants in the environment, and monitoring tools based on molecular biology to detect the catabolic genes and microbes involved in the degradation processes have also been developed⁷⁸⁻⁸⁰. Risk assessment involves studies concerning environmental toxicity of chemicals and VTT has a long expertise in environmental toxicity studies⁸¹⁻⁸³. In addition, VTT has ongoing research in performing physico-chemical analysis of chemicals, modelling of the fate and behaviour of chemicals in the environment e.g. absorption, bioavailability, biodegradability and environmental toxicity. Because the environmental effects of chemicals cannot be confirmed by standard biodegradability and ecotoxicity tests, there is a need for further research to develop simulation tests and to study the behaviour of chemicals in nature.

3.2 Alternative methods for animal testing

The integration of data and test requirements are still under extensive development for the REACH legislation. There are several RIPs ongoing to develop tools and guidance for the new legislation. The major project developing guidelines for testing strategies is RIP 3.3. The first outcome of this project was the FINAL report TAPIR Technical Guidance on Information Requirements⁸⁴ on the intrinsic properties of substances. In this project, several guidelines will be formulated to fulfil the data requirements in REACH. Aspects such as how to utilise existing information and how to formulate a practical guideline for the users are addressed. In order to reduce the number of animal tests, specific testing strategies are under development in several EU-funded RIP projects. Additional goals are the enhancement of the use of computational methods such as QSARS to classify potential hazards of chemicals based on their molecular structure, and also to apply computational techniques more in risk assessment, instead of testing. Testing cannot be completely avoided, however, due to the complex mechanisms involved in biological systems and the environment.

In addition to the legally binding standardised testing methods listed in the Annex V of Directive 67/548/EEC, the TAPIR working group has emphasised the need for guidance for the use of non-guideline toxicity tests, which has not been conducted under GLP, but are performed with valid highly scientific methods. It has also been clearly stated that no single over-arching scheme can cope with the diversity of all the scientific aspects.

Humans are exposed to a multitude of chemicals during their life-time. In addition to the direct exposure to the chemicals such as cosmetics, cleaning agents, pesticides, textiles and household ingredients, we are obviously also exposed to chemicals in our every day life via the environment. Environmental sources for human exposure include the drinking water, food and air. The TAPIR Final report (RIP 3.3) noted that there is a lack of guidance and tools for the assessment of human exposure via the environment. The major exposure routes in human exposure assessment are presented in Figure 1.

The response to chemicals in humans is diverse. Human health effects can either be acute, which means an immediate toxic response, or chronic, where adverse effects are typically observed later in the human lifetime as cancers or other metabolic aberrations. Also, the chemical may have hormonal effects, known as endocrine disrupting properties, which may result in abnormal sexual development, or the reduction in reproductive abilities. Developmental toxicity is generated as abnormal development in the prenatal phase and sickness in offspring.

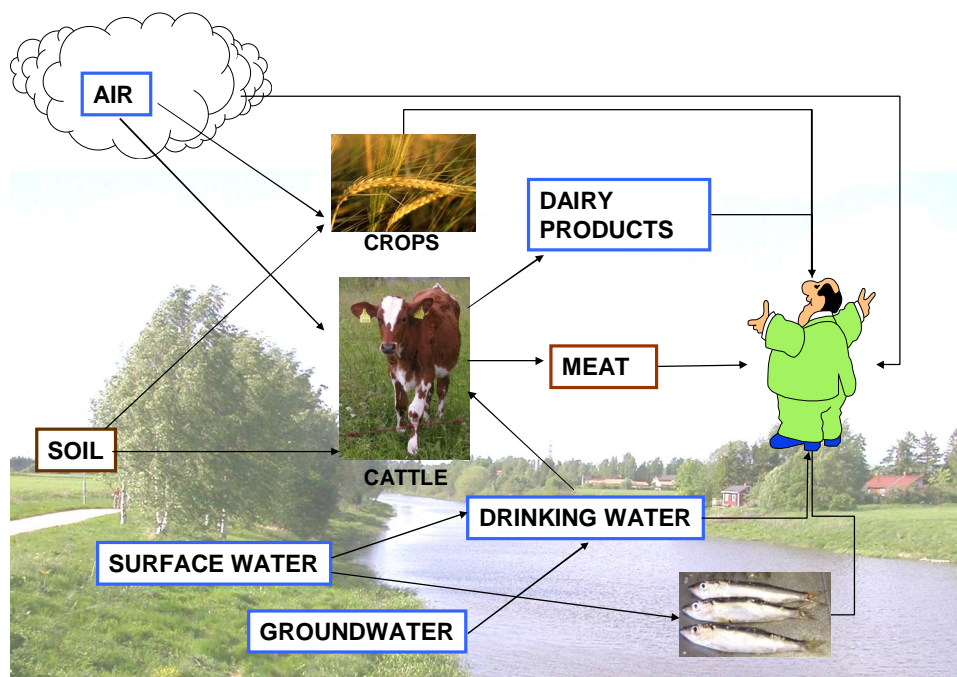


Figure 1. Exposure routes in human exposure assessment⁸⁵.

3.2.1 *In vitro* tests

In vitro tests can be very useful not only when estimating human acute toxicity, but also in assessment of the environmental exposure. The definition of *in vitro* means a test performed "in a test tube". The tests can be cell or tissue culture based, or based on the use of the whole organism, for example, using algae, fish, water flea, or earthworms. The limitations of *in vitro* tests like species-specific toxicity must be acknowledged in the development work. In addition, at present, for example, development toxicity must be performed by using animal tests.

There is intensive ongoing research to develop new *in vitro* tests. *In vitro* tests can be applied as predictive *in vitro* methods as an aim to reduce or replace the animal tests needed for regulatory purposes. Many *in vitro* tests are used as additional tools to provide information of the mechanisms or either applied for diagnostic purposes. Tests which are aimed at regulatory purposes have to undergo a validation process to confirm their reliability; Table 5 presents the tests which have been validated for regulatory purposes. In Europe, the process of validation of new tests is coordinated by ECVAM. The validation is also coordinated within the OECD Test Guidelines Programme and by various other organisations.

In vitro tests can be used successfully as screening tests to reduce the need for further testing or to reduce the amount of animal testing. *In vitro* tests have been considered useful in providing more information on the toxicological mechanisms, especially in the identification of genotoxic chemicals⁸⁴. Mutagenicity and genotoxicity tests are well-established and accepted for the tiered testing approach. New methods are under development, such as micronucleus test *in vitro*, Comet assay, Big Blue Rat and MutaMouse, where photo-genotoxicity is already applied in cosmetics testing.

Table 5. *In vitro* tests which have been scientifically validated and *in vitro* tests which have received regulatory acceptance^{86,87}.

Scientifically validated methods	Regulatory acceptance
<ul style="list-style-type: none"> • Five <i>in vitro</i> Pyrogen Tests ESAC statement • Testing Strategy to Reduce the Use of Fish in Acute Aquatic Toxicity Testing ESAC statement • The Colony Forming Unit-Granulocyte/Macrophage (CFU-GM) Assay for Predicting Acute Neutropenia in Humans INVITTOX Protocol, ESAC Statement • ELISA test for batch potency testing of erysipelas vaccines ESAC Statement • Embryonic stem cell test for embryotoxicity INVITTOX Protocol, ESAC Statement • Micromass embryotoxicity assay INVITTOX Protocol, ESAC Statement • Whole rat embryo embryotoxicity assay INVITTOX Protocol, ESAC Statement • CORROSITEX assay for skin corrosivity Date of the ESAC statement: 06 December 2000 - The ESAC statement is based on the outcome of the US NTP-NICEATM study. INVITTOX Protocol, ESAC Statement • ELISA test for batch potency testing of tetanus vaccines for human use ESAC Statement • Toxin Binding Inhibition (ToBI) test for batch potency testing of tetanus vaccines for human use ESAC Statement • Local Lymph Node Assay for skin sensitisation (LLNA) Date of the ESAC statement: 21 March 1999 - The ESAC statement is based on a retrospective data analysis. ESAC Statement • 3T3 Neutral Red Uptake (NRU) photo-toxicity test INVITTOX Protocol, ESAC Statement • <i>In vitro</i> production of monoclonal antibodies - The ESAC statement is based on a retrospective data analysis. ESAC Statement • EpiSkin™ skin corrosivity test INVITTOX Protocol, ESAC Statement • Rat Transcutaneous Electrical Resistance (TER) skin corrosivity test INVITTOX Protocol, ESAC Statement • EpiDerm™ skin corrosivity test INVITTOX Protocol, ESAC Statement 	<ul style="list-style-type: none"> • EpiSkin™ skin corrosivity test - Included into Annex V 67/548/EEC, OECD • 3T3 NRU photo-toxicity test - Included into Annex V 67/548/EEC, OECD • EpiDerm™ skin corrosivity test - Included into Annex V 67/548/EEC, OECD • Rat TER skin corrosivity test - Included into Annex V 67/548/EEC, OECD • <i>In vitro</i> tests for percutaneous absorption OECD • Deletion of the acute oral toxicity test, Lethal Dose (LD50) - The method has been deleted from both the Annex V 67/548/EEC (Method B.1.), as well as from the OECD Test Guidelines 67/548/EEC, OECD • Local Lymph Node Assay for skin sensitisation (LLNA) OECD, U.S. EPA OPPTS • ELISA test for batch potency testing of erysipelas vaccines EDQM/European Pharmacopoeia • ELISA test for batch potency testing of tetanus vaccines for human use EDQM/European Pharmacopoeia • Toxin Binding Inhibition (ToBI) test for batch potency testing of tetanus vaccines for human use EDQM/European Pharmacopoeia

An emerging toxicological research field is toxicogenomics, which is the use of 'omics' technologies such as genomic scale mRNA expression (transcriptomics), cell and tissue-wide protein expression (proteomics) and metabolite profiling (metabolomics), and bioinformatics to analyse the data.

Toxicogenomics would be useful by providing information of biomarkers and providing more understanding of the mechanisms of toxicity. Ecotoxicogenomics would provide information on the variation of responses of different trophic level organisms to chemical exposure. The future applications and use of toxicogenomics for regulatory purposes has been evaluated recently by an OECD/IPCS Expert Group. The responsibility of this group in the future is to develop the policy for the evaluation and use of 'omics' data for regulatory purposes.

The science of *in vitro* toxicology is relatively young, but it is growing exponentially. The challenge for the years ahead is to incorporate the mechanistic knowledge generated by cellular and molecular studies into the vast inventory of *in vivo* data to provide a more complete description of toxicological mechanisms, as well as to establish a paradigm by which *in vitro* data may be used to predict toxicity *in vivo*.

VTT has extensive expertise in several areas related to this topic; e.g. the development of *in vitro* tests based on cell and tissue cultures and development of 'omics' techniques for studying gene expression in human and environmental applications. System biology combined with environmental exposure and ecotoxicological studies could be applied as dose response studies in the future.

Cell-based screening to substitute animal testing

Cell-based screening is aiming at the identification and validation of drug discovery targets, the evaluation of the efficacy and toxicity of drug molecules, and the optimisation of the lead molecules. Analysis of the vital phenotypic properties of living cells like cell proliferation, apoptosis, or the activation of the specific marker genes within the signalling cascades provides direct functional biological information.

The effects of various toxic compounds can be categorised based on their molecular signatures in living cells. These signatures can include gene expression, metabolomics, lipidomics or proteomics profiles. By correlating chosen phenotypic changes of living cells to predetermined profile libraries, it will be possible to establish a rapid and efficient screening method for the analysis of chemical compounds. The rapid screening method would allow a preliminary evaluation of particular compounds in high throughput mode. This improves the overall cost effectiveness of testing needs in REACH, because of the rapid preselection allows to focus further testing on compounds having toxic profiles.

The cell-based assays provide valuable information on the causal relationships of the gene-chemical interactions, which is especially important in assessing the toxicity of compounds. The VTT Medical Biotechnology group has set up high-throughput instrumentation for cell biology research. The instrumentation enables the analysis of tens of thousands of experiments, for example, screening of large number of compounds with a number of cell lines. The hardware configuration is built around a liquid and plate handling robot, onto which the cell culture incubator and the measurement devices are integrated. One of the integrated instruments is the Acumen Explorer™ cell-based fluorescence scanner; combining the advantages of an image-based cytometer, a plate reader and a fluorescence microscope scanner. The instrument is capable of simultaneous and very fast measurement of three different parameters representing the cell phenotypic properties: the analysis of one microtiter plate lasts for approximately fifteen minutes, and thus enables the scanning of up to 10 000-30 000 experiments per day (representing the efficacy needed in cell-based screening for REACH applications).

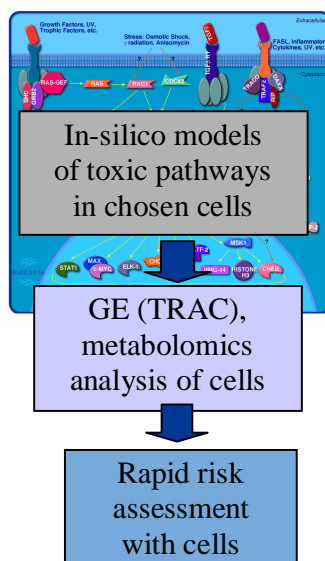


Figure 2. The process of defining toxic fingerprints with living cells. The fingerprints are based on molecular profiles, such as gene expression (GE), metabolic, lipidomic and proteomic profiles.

The aim of VTT's cell screening laboratory is to develop new screening methods, which could be utilised in various applications, and especially in customer-oriented contract research. The research laboratory has been started with the activities focusing on setting up cell-based assays for cancer research, whilst also developing the technological readiness for other applications. In the first place the high-throughput instrumentation is used to not only automate the traditional microtiter plate-based cell assays, but also to accelerate the process further by miniaturising the procedures into the cell array format.

3.2.2 *In silico* methods

Quantitative structure-activity relationships (QSARs) are mathematical models for approximating the often complex relationships between the chemical properties and the biological activities of compounds. It is convenient to distinguish between QSARs and SARs: QSARs are typically quantitative in nature, producing categorical or continuous prediction scales; SARs are qualitative in nature, often occurring in the form of structural alerts that include molecular substructures or fragment counts related to the presence or absence of biological activity. QSARs dealing with physico-chemical properties are also commonly referred to as QSPRs. Both QSARs and SARs are *in silico* methods (that rely on calculations done by a computer) and are also commonly referred to as QSARs.

The fundamental principle of all QSARs lies with the assumption that all the information that determines the chemical, biological and physical properties of any compound is included or "coded" in the compound's structural formula. It is further anticipated that, within a series of compounds having their biological activity expressed via the same mechanism, a change in the chemical structure will be accompanied by a proportionally small shift in biological activity, and with a proper set of descriptors the structure-activity relationship can be mathematically described. These relationships tend to be of a local nature, and generally there is a trade-off between the chemical diversity of training set compounds and the complexity of the biological response studied, i.e. complex mechanisms can be modelled for small subgroups of chemicals only.

The basis for modern QSAR models⁸⁸ as laid out by Corwin Hansch, who suggested a linear relationship^{89,90} between the logarithm of the inverse toxicant concentration and terms arising from hydrophobic, electronic and steric⁹¹ effects. In the simplest case of non-specific narcotic toxicity, the electronic and steric effects may be neglected⁹² and a linear relationship between the logarithmic concentration and water/octanol partition coefficient is obtained. While these simple linear relationships, often with limited range of applicability, provide little value alone, a computer software equipped with thousands of such equations⁹³ can be utilised for larger scale screening applications. Other QSAR approaches include the use of software such as MultiCASE⁹⁴, TOPCAT⁹⁵, OASIS⁹⁶ and CATABOL⁹⁷, as well as statistically based methods⁹⁸ relying on multiple linear regression, principal component analysis (PCA), principal component regression (PCR), partial least squares (PLS), and neural network analysis.

The possibility to apply QSARs in the regulatory assessment of hazardous properties of substances is recognised in the REACH regulation as long as the methods used are scientifically validated and well documented. It is hoped that the use of these models will reduce considerably the testing costs and the amount of animal testing needed, as well as speed up the entire testing process. According to cost estimates⁹⁹ based on different levels of acceptance of QSAR estimations, the total estimated testing costs of the REACH regulation will be 1180 M€ and 2423 M€ for the minimum testing needs and maximum testing needs, accordingly. The largest amount of testing will be required for skin sensation, eye irritation and *in vivo* mutagenicity, and in general the studies related to human health endpoints are the most expensive (anticipated to be about 86% of all the testing costs). For the reasons mentioned above, there is currently a very strong demand to promote the development, validation and implementation of QSAR models, and the ECB is actively involved in this field of research.

The worldwide regulatory use of QSAR models has been reviewed recently^{100,101}. QSAR models are intensively used in the United States, but not at all in Japan and Australia. The use of QSAR models within the EU member states varies considerably between the different national regulatory authorities. To promote the regulatory use of QSAR models within the EU member states, guidelines and acceptability criteria for the use of QSAR models are clearly needed¹⁰². General validation principles, including case study examples, have been presented in the OECD QSAR expert group report¹⁰³, and a more detailed general QSAR validation principles guideline has just been released by ECB¹⁰⁴.

The basic principles a QSAR model should meet for the validation for regulatory purposes are^{103,104}: 1) a defined endpoint, 2) an unambiguous algorithm, 3) a defined domain of applicability, 4) appropriate measures of goodness-of-fit, robustness and predictivity, and 5) a mechanistic interpretation, if possible. A QSAR can be defined as a qualitative or quantitative relationship between chemical structure and the physical property or activity being modelled. The property or activity being modelled is called the "endpoint" and the equation or relationship yielding the desired property from the molecular structure and other data is called the algorithm. It should be clearly stated which property is being modelled, and under which experimental conditions, and the algorithm used for the modelling should be transparent so that the end-user can understand how the estimated value was generated. The applicability domain of a QSAR model is defined as "the response and chemical structure space in which the model makes predictions with given reliability". For a detailed discussion on QSAR applicability domains the reader is referred to the recent ECVAM workshop report¹⁰⁵. The internal performance of the model should be validated statistically (goodness-of-fit and robustness) and the external performance of the model (predictivity) should be validated by using an external test set of chemicals not included in the training set used to derive the model. If data for such an external test set is not available, an internal validation can be performed using, for example,

cross validation or bootstrapping techniques¹⁰⁶. Finally, the model should be constructed using descriptors that are easily interpretable and can be reasoned to have a significant effect on the endpoint being modelled¹⁰⁷. Reviews of some commonly used descriptors can be found in the literature^{108,109}.

The OECD QSAR expert group report contains a basic checklist of whether the principles listed above (sometimes referred to as the Setubal principles, named after a conference held at Setubal, Portugal in 2002) are fulfilled for some current models dealing with acute fish toxicity, atmospheric degradation, mutagenicity and carcinogenicity and QSARs for predicting the NOEL in humans, as well as a similar checklist for the use of software such as ECOSAR¹¹⁰, DEREK¹¹¹, Japanese Chemicals Evaluation and Research Institute (CERI) biodegradation expert system¹¹² and TOPCAT⁹⁵. Additional guidance on the use of QSARs in environmental risk assessment can also be found in the EU Technical Guidance Document on Risk Assessment¹¹³. However, no criteria for the validity and acceptability of any of these models, nor any criteria for the regulatory use of them, have been given in these documents. A separate document for the regulatory applications of QSARs is currently being developed by the OECD^{114,115}.

The use of QSAR models for aquatic toxicity^{116,117}, and for eye¹¹⁸ and skin¹¹⁹ irritation/corrosion has recently been studied by ECB and the National Institute of Public Health of the Netherlands. Simple physico-chemical exclusion rules were determined for eye and skin irritation, and an external validation of the models was carried out. The model for skin irritation was found to produce nearly 100% correct predictions, and it was estimated that the model could be used to waive at least 43.2% of the skin irritation tests for new chemicals. These results clearly show the potential of QSAR models, and it is hoped that the further development of these models would result in waiving nearly all of the tests for low production volume chemicals⁹⁹. However, a lot of work needs still to be done before end-user level tools for the assessment of hazardous properties of chemicals can be presented.

The ECB has taken the initiative to build an internet-based inventory database of available QSAR models¹²⁰, with descriptions needed to judge the validity of the model for the endpoint studied, and guidance on the interpretation of the estimated data. A scoping study of such an internet-based QSAR decision support system has already been prepared¹²¹, and the first internet version of the Danish QSAR database¹²² with about 70 different QSAR models was published in 2005. The current QSAR database, however, does not contain any experimental data or information about the models themselves¹²³, whereas the final QSAR application toolbox¹²⁰ will be integrated with the European chemical Substances Information System (ESIS)¹²⁴ and will also contain information about the models and their validity. The ECB is also sponsoring the development of the ToxTree¹²⁵ software for chemical hazard classification using decision trees, and the Similarity tool¹²⁰ software for estimation of several endpoints by read-across techniques. Further computer software related activities of the ECB¹²⁶ include validation of the TerraQSARTM FHM model¹²⁷ and beta testing of AIM (Analogue Identification Method, developed for the U.S. EPA) and AMBIT¹²⁸. Naturally, the ECB also carries out work with developing and validating QSAR models¹²⁹⁻¹³¹, but with its current workload many of the evaluation studies¹³² have been outsourced.

While waiting for the practical guidelines of QSAR model usage for the regulatory level, the models can still be used for other purposes. For example, the approach of Danish EPA with predicting the acute oral toxicity, skin sensitisation, mutagenicity, carcinogenicity and aquatic environment hazards of nearly 47 000 chemicals at once¹³³, may be used for prioritising chemicals testing.

4 Determination of hazardous properties of chemicals

Chemicals, through the different stages from their production to their handling, transport and use, are a real danger for human health and the environment. To be able to manage this danger, identifying and assessing the possible hazards of chemicals is required. Hazard assessment is carried out considering all the possible effects of concern of the substance evaluated, and the chemical is classified and labelled according to GHS⁷¹ in order to give a clear and simple description of the appropriate effects of the chemical to the end users. Hazard identification and assessment is the first step towards the complete risk assessment of a chemical, and is based on the intrinsic properties of the chemical, not on the risks of the chemical usage.

4.1 Hazard identification and assessment

A chemical can have properties that are physical hazards, health hazards or hazards for the environment. Physical hazards include the flammable, combustible, explosive, oxidising and pyrophoric properties of the chemical, as well as hazards related to compressed gases and organic peroxides. The classes of health hazards include:

- carcinogens,
- reproductive toxins,
- sensitisers,
- hepatotoxins (liver toxin),
- agents that act on the hematopoietic system (blood),
- agents that damage the lungs, skin, eyes, or mucus membranes,
- irritants,
- corrosives,
- neurotoxins (nerve),
- nephrotoxins (kidney).

The basic elements of hazards for the environment are acute and chronic aquatic toxicity, bioaccumulation and bioconcentration, and the degradation properties of organic molecules.

There is a massive EU Technical Guidance Document on Risk Assessment available on the ECB's website. This Technical Guidance Document is divided into four parts dealing with risk assessment related to human health endpoints⁷⁰, environmental risk assessment¹³⁴, the use of QSARs¹¹⁴ and emission scenarios¹³⁵, and contains valid guidelines for chemical hazard assessment under the REACH regulation. While it is impossible to give a complete review of this document within the scope of this text, we will still try to highlight here some of the main points related to chemical hazard assessment.

The chemical hazard assessment includes both the identification of the possible hazards and a dose-response assessment, in which the level of exposure to the chemical and the severity of the effects arising from the exposure are analysed. The effects assessment is carried out by listing all the available, relevant data, from human and animal testing, *in vitro* studies or theoretical studies and weighting the relevancy and reliability of the data with respect to the endpoint studied. This data evaluation is particularly important for well-studied existing substances where there may be a number of different test results available for some endpoints, but some of the tests may not have been carried out according to current standard methods. The dose-response assessment step should also include predictions for the NOAEL or for LOAEL, when possible. If it is not possible to determine

N(L)OAEL for an effect, it is sufficient to evaluate whether the substance has an inherent capacity to generate such an effect.

If there is both animal and human test data available, well reported relevant human data is preferred for the hazard assessment of endpoints related to human health. However, the usefulness of human data may be limited by relatively low exposure levels, poor reporting, lack of information on exposure effects, small number of subjects, etc. Especially the reports dealing with the effects arising from accidents or abuse of a chemical may lack sufficient information on the exposure level, but it is still sometimes possible to derive a minimum lethal dose from these reports. Exposure effects on humans generally vary considerably from person to person, and therefore negative data from human studies will not usually be used to override a classification that has already been made from valid animal studies, unless the classification is based on an effect that is not expected to occur in humans. Studies using human volunteers are strongly discouraged because of ethical problems, but if there is good quality data from human volunteer studies already available, it can be used in justified cases. Such studies have to be conducted in line with the World Medical Association Declaration of Helsinki¹³⁶, which describes the general ethical principles for medicinal research involving human subjects.

The animal testing and *in vitro* studies carried out according to current methods (EU Annex V, OECD or U.S. EPA) and reported appropriately are considered the most reliable for hazard assessment, particularly if conducted in accordance of the GLP principles. If such studies are not available, other studies may also be used, especially if results from a batch of different studies are consistent. If the results from a batch of studies are inconsistent, the rapporteur needs to decide which studies are the most reliable. Toxicokinetics data (including metabolism data) of the chemical in both humans and animal species should be used, whenever available, to evaluate the relevance of data from animal studies for human health endpoints.

The use of QSARs can prove useful in cases where the data is limited or the data reliability is questionable. Experimental data is generally preferred, but in some cases QSARs can even be used to estimate an endpoint when experimental data does not exist. Guidelines for the use of QSARs in estimating environmental endpoints are presented in the third part of the EU Technical Guidance Document on Risk Assessment¹³⁴, and examples of the use of QSARs in environmental endpoint estimation can be found in the existing chemical risk assessment reports^{137,138}. Guidelines for the use of QSARs in estimating endpoints related to human health are still being prepared by OECD, but it is clear that once these guidelines and the OECD QSAR database are available, the use of QSAR models will become common practice.

4.2 Classification and labelling

The Globally Harmonized System of Classification and Labelling of Chemicals (GHS)⁷¹ is planned to be introduced in the near future, in parallel with REACH. In short, GHS basically merges the classification and labelling approaches now in place for the storage of chemicals on the one hand, and transportation of chemicals on the other.

GHS is the culmination of more than a decade of work. There were many individuals involved, from a multitude of countries, international organisations, and stakeholder organisations. Their work spanned a wide range of expertise, from toxicology to fire protection, and ultimately required extensive goodwill and the willingness to compromise, in order to achieve this system.



The international mandate that provided the impetus for completing this work was adopted in the 1992 United Nations Conference on Environment and Development (UNCED): "A globally harmonized hazard classification and compatible labelling system, including material safety data sheets and easily understandable symbols, should be available, if feasible, by the year 2000".

While governments, regional institutions and international organisations are the primary audiences for the GHS, it also contains sufficient context and guidance for those in industry who will ultimately be implementing the national requirements which are adopted. The availability of information about chemicals, their hazards, and ways to protect people, will provide the foundation for national programmes for the safe management of chemicals. Widespread management of chemicals in countries around the world will lead to safer conditions for the global population and the environment, while allowing the benefits of chemical use to continue. Harmonisation will also have benefits in terms of facilitating international trade, by promoting greater consistency in the national requirements for chemical hazard classification and communication that companies engaged in international trade must meet.

Being an international agreement, there is currently no further need for research in this area. One may expect that in the future there might be a need to study the adoption of the new system by industry and the employees using the chemical products.

5 Chemical Safety Assessment (CSA)

If a chemical is classified as dangerous after evaluating its health, environmental and physico-chemical hazards, as well as possible PBT or vPvB properties of the substance, the conditions in which the chemical can be safely used has to be defined. According to the REACH proposal, this will be performed in the exposure assessment step.

The next step after the intrinsic chemical hazards of a substance have been assessed is to estimate the risk or likelihood of harm occurring when using the chemical for specific purposes. Risk characterisation considers both the chemical hazard and the exposure to the chemical, and may be presented by a simple formula:

$$\text{Hazard} \times \text{Exposure} = \text{Risk}$$

To show that risks can be adequately controlled, the manufacturer or importer should develop ESs as part of the exposure estimation. An ES gives realistic conditions under which the substance is manufactured or used (identified uses). It prescribes appropriate or suitable RMMs that shall be in place during manufacture or use of a substance, including the entire life cycle of the substance. The ES is needed for risk management at the various life cycle stages to ensure the safe handling and adequate control of risks related to human health (workers and consumers) and the environment.

5.1 Estimation of the risk for humans

An ES is a description of a control strategy for substances, giving realistic operational conditions for the manufacture of a substance, or identified use(s) of a substance, a group of substances or a preparation. It prescribes appropriate RMMs that shall be in place during manufacture or use of a substance, including the service life and waste phase, under a given set of operational conditions.

Exposure assessment aims to determine the:

- a) Type and conditions of use and measures under which safe use throughout the supply chain is possible,
 - b) Quantification of the exposure likely to occur under the conditions described in the ES,
- and comprises the following steps.

Firstly, it establishes whether an exposure assessment is required. If the chemical is classified as dangerous, an initial ES containing also the relevant RMMs is developed. This ES is based on the available information. Subsequently, the level of exposure is estimated taking into account the exposure relevant properties of the substance. The estimate of the exposure is compared to the Derived No-Effect Level (DNEL) or Derived Acceptable Exposure Level (DAEL) in a risk characterisation process. If necessary, the ES is refined – especially when improved exposure and hazard information does not lead to adequate control.

5.2 Development of Exposure Scenarios (ES)

The ES is a communication tool for downstream users (DUs) to help them adequately control risks while using the chemical or preparation. The development of the ES is an iterative process which continues until the conditions where the adequate control of risks can be demonstrated. The main outcome of the CSA is the ES and the appropriate RMMs to be communicated to the users of the chemical. The development proceeds according to the following steps:

- a) Identification of uses and use processes,
- b) Description of manufacturing or use processes,

- c) Development of a "tentative" ES,
- d) Assessment of exposure and risks,
- e) Definition of the "final" ES, and
- f) Development of the Annex to the SDS.

A proposed strategy for the identification of uses and use processes includes:

- Usage of in-house information,
- Use of publicly available information, and
- Communication with the DUs.

Recognised problems may occur when the communicated information includes particular details on the DU's processes which are considered to be CBI.

VTT has excellent information services and can provide the information needed for constructing the ES. It can offer, for example, publicly available information sources to identify uses, search for available information on the properties of the substances, information concerning the exposure, and also information regarding the available RMMs. VTT also has extensive in-house information on chemical uses around the world.

The development of different kinds of information systems, which can be used to facilitate the communication between the manufacturers/importers and the DUs, while taking into consideration any relevant CBI, is also an area in which VTT has expertise.

The description of manufacturing or use process involves the identification of a list of exposure determinants. Also the manufacturing and use processes are identified and described. The determinants of exposure are used to ensure that the ES covers the relevant exposures. The set of basic assumptions on the operational conditions are defined, and the RMMs that would secure an adequate control of the risks to human health (workers, consumers) and the environment are determined.

Because the exposure is dependent on a number of main determinants, information regarding these determinants is very important in order to understand the scope of the ES, as well as to enable the checking of its adequacy. The number of determinants of exposure is very large and several authors have attempted to describe and cluster exposure determinants. This is generally done for specific types of work or specific forms of exposure^{139,140}. Also, VTT has performed research work on determinants of exposure such as the identification of factors affecting styrene exposure¹⁴¹ and factors affecting the substance to become airborne^{142,143}. VTT has also participated in the development of video exposure monitoring tools (e.g. PIMEX) and their effective utilisation in occupational hygiene work¹⁴⁴. The PIMEX tool is suitable for detecting factors affecting the exposure, as well as for factors affecting the efficiency of risk management methods. Other not commonly measured properties of the substance, such as dustiness of powders, can also be measured. It is obvious that more information on the determinants of exposure is needed, especially when more detailed ESs (e.g. more detailed exposure modelling) have to be performed.

The development of an ES is an iterative process. Firstly, a "tentative" ES for the process is developed. The description would normally be relatively simple and it is based on the available data. It describes the exposure situation and typical operational conditions, and should include the RMMs normally utilised with the process. When the ES is described, the exposure based on these assumptions is estimated. The utilisation of exposure models such as ECETOC TRA or

RISKOFDERM, and a tiered approach, is recommended during this phase. However, more development is needed, especially in the higher tier and for more specific ESs.

The efficiency of implemented RMMs should be catered for in the exposure estimates, and this makes the assessment even more difficult. This could be an insurmountable task especially for SMEs and DUs, and therefore, other types of approaches may be more suitable. The UK Health and Safety Executive's COSHH Essentials^{145,146} and the ILO Chemical Control Toolkit¹⁴⁶ are tools which attempt to guide users towards suitable RMMs. These tools guide the choice of the RMMs based on the properties of the substance (health hazards, fugacity) and the quantity of the substance used, and the process in which the substance is used. And the "exposure assessment" is actually hidden from the users.

VTT's Kemi-Arvi¹⁴⁷ 3.1 belongs to the latter tool category. Kemi-Arvi is designed to help companies, especially SMEs, assess whether their chemical risks are adequately controlled – based on the properties of the substance, the route of exposure, the handling of chemicals, the technical control measures or PPE implemented, and the organisational measures in use. The tool is question-based and very easy to use. It covers both continuous occupational exposure, as well as accidental exposure. The suitability of these risk management-oriented type of tools should be tested, however. The Kemi-Arvi tool may also be used in ES building, after some further development.

A third approach to building ESs is with the utilisation of exposure measurements and exposure databases. VTT has also been involved in the utilisation of exposure databases; for instance, when the occupational exposure to the styrene monomer in Finnish industry was assessed^{148,149}. In addition, VTT has a long tradition in measuring both occupational and non-occupational exposure to chemicals, as well as identifying their sources and source strengths¹⁵⁰⁻¹⁵⁶. The Finnish Institute of Occupational Health (FIOH) maintains the unique FINJEM job exposure matrix database. It has been widely used in epidemiological studies, but the suitability for developing ESs could also be investigated.

5.3 Estimation of environmental risk

The aim of the risk assessment is to obtain information on the undesired phenomena which are to be minimised or totally eliminated by suitable measures. In the CSR the producer must also show that the risks are adequately controlled, which means that the influence of management methods on risk has to be estimated. Therefore, the risk assessment of chemicals is usually an iterative process (Figure 3).

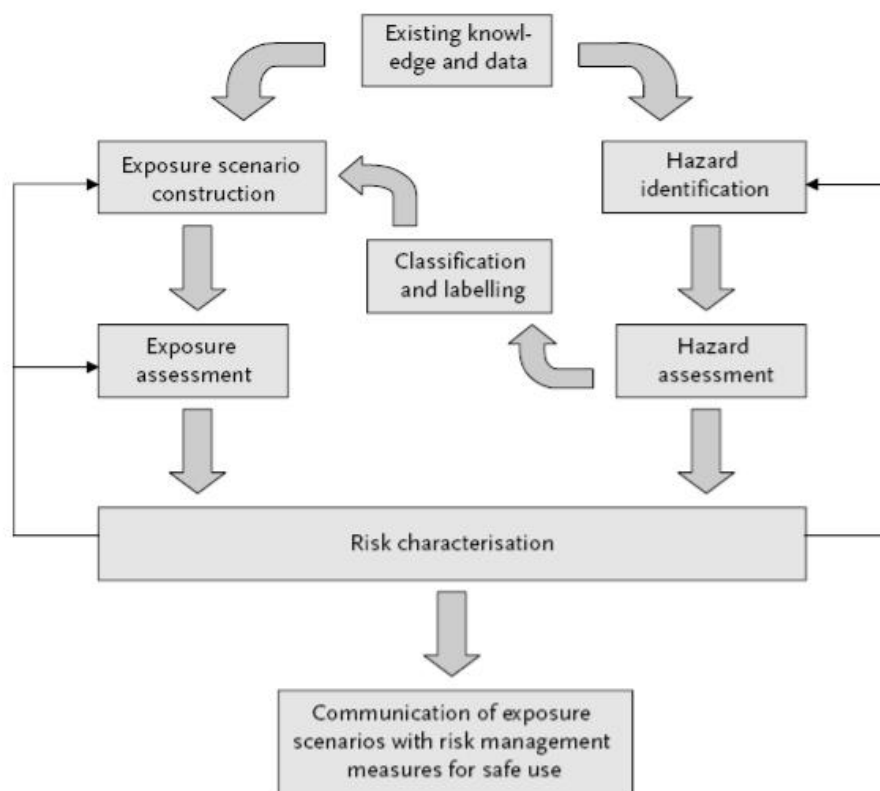


Figure 3. Hazard and risk assessment stages of a CSA¹⁵⁷.

Environmental risk assessment and characterisation generally include the following steps:

a) Hazard identification

Identification of adverse effects of the chemical to various organisms (e.g. water and soil organisms, plants, vertebrates) and ecosystems using existing data, testing and modelling methods, etc.

b) Construction of exposure scenarios

The ES shall include all identified uses and all steps of the entire life cycle of the substance, such as production, handling, storing and disposal, as well as the impact of RMMs. ESs describe how substances are manufactured or used during their life cycle and how the manufacturer or importer controls, or recommends to control exposures of humans and the environment. This means that information on the emission of the dangerous substances to, for example, air, water (sediment), soil and sewage treatment system, is needed.

c) Estimation of emissions to the environment

d) Exposure assessment

Exposure assessment includes the estimation of emissions, their transport or fate, and doses of relevant exposed subjects and dose-response assessment. For example, the following exposure pathways are considered relevant with regard to the production and use of chemicals:

- influence on plants, soil micro-organisms, invertebrates and vertebrates in direct or indirect contact with the product,
- accumulation of toxic compounds through the food chain,
- influence on the ground and surface water quality and water organisms during the entire life cycle (i.e. storage, transport, use, disposal),

- influence on sewage treatment processes.

e) Risk characterisation

Risk characterisation means that all the unfavourable properties or conditions are listed and described, and an estimate of the incidence and severity of any adverse effects is made. The risk assessment also covers the assessment of the impacts of undesired phenomena.

f) Evaluation of uncertainty

An important part of the risk assessment is to evaluate the impact of critical parameters on the results. Numerous uncertainties are involved in the use of scenarios, the interpretation of test data, the integration of different data sources, and understanding the effects resulting from exposures to mixtures of chemicals, coupled models, and assumed or averaged parameters and data.

The EU's Joint Research Centre (JRC) has produced a revised version of the EU Technical Guidance for Risk Assessment¹³⁴. The guidance is produced in support of existing directives and regulations on risk assessment of new notified and existing substances and biocidal products. For example, the following issues are included in the report:

- How to calculate Predicted Environmental Concentrations (PECs) and Predicted No-Effect-Concentrations (PNECs) and, where this is not possible, how to make qualitative estimates of environmental concentrations and effect/no effect concentrations;
- How to conduct a PBT (persistence, bioaccumulation and toxicity) assessment;
- How to decide on the testing strategy, if further tests need to be carried out and how the results of such tests can be used to revise the PEC and/or the PNEC.

Guidelines for the risk assessment of contaminated sites have also been developed and can in many cases be the basis for the evaluation of environmental risks. In the risk assessment of contaminated sites, the effects are estimated retrospectively after the chemicals are released in the environment. Local and site-specific aspects are more or less considered which may, however, be very challenging in the environmental risk assessment. Chemical risk assessment is prospective by nature, and as such usually generic rather than site-specific.

VTT has a long experience in the assessment of environmental risks of contaminated sites, landfill disposal of waste and utilisation of industrial waste in earthworks, as well as risk assessment of nuclear waste disposal alternatives¹⁵⁸⁻¹⁶⁴. The most important expertise areas include:

- Investigation and assessment of the emissions of toxic chemicals leaching from various materials (e.g. soil, by-products and wastes, construction products, ores and minerals) using leaching tests and leaching models,
- Transport models,
- Combination of leaching data and transport modelling,
- Estimation of emissions to air,
- Ecotoxicological tests,
- Management of risk assessment projects,
- Environmental exposure scenarios,
- Life-cycle assessment of processes and products.

As mentioned above, the general principles and methodologies of contaminated soil risk assessment are mostly applicable for other chemical-containing materials and products in both prospective and retrospective assessments. VTT has used these guidelines, for example, for the assessment of risks arising from the utilisation and disposal of wastes and construction products.

Table 6 describes the research needs and VTT's competencies related to the environmental risk assessment of chemicals.

Table 6. Research needs and VTT's competencies in environmental risk assessment.

Title	Information needed, tools available	Research needs	VTT competence
General	Overall scheme	<ul style="list-style-type: none"> Development of framework for risk assessment 	<ul style="list-style-type: none"> Management of risk assessment projects
Hazard identification and assessment	Toxicity to water and soil organisms, plants, micro-organisms and vertebrates <ul style="list-style-type: none"> Ecotoxicological tests, QSAR and other modelling methods 	<ul style="list-style-type: none"> Development and use of molecular modelling, QSAR, etc. methods to minimise animal testing Improvement of integrated application of various information types (testing, QSAR, grouping, other existing information). 	<ul style="list-style-type: none"> Ecotoxicological tests, interpretation of test results Development of modelling tools Expertise on molecular modelling
Description of scenarios	<ul style="list-style-type: none"> Selection of substances of concern, information on material and product properties, and process conditions Identification of harmful properties during the entire life cycle of the chemical and all its identified uses, including the most important handling steps 	<ul style="list-style-type: none"> Guidelines for the justification of selected scenario and input data 	<ul style="list-style-type: none"> Experience on life-cycle assessment of processes and products Knowledge of production and downstream use processes of inorganic and organic chemicals Expertise on emission estimation (process and diffuse emissions)
Identification of relevant exposure routes	<ul style="list-style-type: none"> Descriptions of process and operational conditions Risk management measures 		
Evaluation of emissions to environmental compartments and exposure of critical targets	Transport by water: <ul style="list-style-type: none"> Emissions to water Choice of appropriate leaching test. This means that the mobility of the substance from the product and also the factors controlling the leaching need to be assessed; usually through a full characterisation of the leaching behaviour. Suitable test methods for the assessment are under preparation in the standardisation organisation of CEN (CEN TC 292). Use of transport models. Several transport models available. Most commonly used groundwater transport tools include: WHI Unsat Suite, FEFLOW, Visual MODFLOW Pro, MOFDLOW-SURFACT, FLOWPATH II, FRACTRAN, FRAC3DVS, MIKE SHE, Risc WorkBench Transport in air: <ul style="list-style-type: none"> Estimation of emissions to air 	<ul style="list-style-type: none"> Development of guidelines for modelling and selection of input-data (model includes several assumptions). Special attention needs to be paid to the differences between the conditions of the real case and of the model presented. Information for the environmental assessment of organic pollutants taking into account their special properties (degradation, colloid formation) Validation studies needed 	<ul style="list-style-type: none"> Extensive experience in the development of tools for mobility studies for soil, waste and products (e.g. leaching tests) and models for test result interpretations Guideline for appropriate modelling Extensive experience on the use of various transport models Estimation of emissions to air, soil and water both from processes and from diffuse sources

Title	Information needed, tools available	Research needs	VTT competence
Risk characterisation	<ul style="list-style-type: none"> Calculation of critical doses for target groups The assessment of ecotoxicological risks can only be made roughly, because only limited suitable reference values for no-observed effect concentrations (NOECs), predicted no-effect concentration (PNEC) or lowest observed effect level (LOEC) are available. 	<ul style="list-style-type: none"> Guidance on the evaluation of exotoxicological risks (methods, reference values) The reference values are usually derived for certain laboratory conditions and certain chemical compounds. The applicability of these values may be poor and therefore they should be used with caution. The ecological effects on plant and animal species are evaluated by comparing the calculated values with the toxicological values reported in literature. 	
Accidents	<ul style="list-style-type: none"> Especially concerning transport (soil & groundwater pollution), fires (soil, groundwater, air) 		<ul style="list-style-type: none"> Dispersion modelling of chemicals Fire emission modelling
Uncertainty analysis	<p>Variations in input data and checking the influence of critical assumptions give important information on the sensitivity of the results.</p> <p>Examples of typical parameters to be checked are:</p> <ul style="list-style-type: none"> influence of product properties (e.g. density, permeability, thickness, chemical composition and leaching behaviour) on doses dilution factor for leachate from the application with environment, i.e. assumptions in the calculation of water flow (rate, percolation, surface wash) 	<ul style="list-style-type: none"> Validation of the model work. 	Experience on the tools used for uncertainty analysis, e.g. Monte-Carlo analysis
Risk management methods	<ul style="list-style-type: none"> Development and assessment of the applicability of risk management methods Assessment of risk reduction by various risk management methods 		<ul style="list-style-type: none"> Development and assessment of technical methods for risk management during chemical production and downstream uses Cost-benefit analyses
Conclusions	Good documentation including relevant input data and assumption. The conclusions and the chosen acceptance criteria need to be carefully explained	<ul style="list-style-type: none"> Development of guidance document for proper and transparent documentation 	

The guidelines developed for contaminated sites are often very broad and general; covering all kinds of exposure pathways to humans and the environment. All the exposure pathways are generally not necessary to consider for the use of industrial chemicals in all applications. For a contaminated site assessment, a tiered approach is usually adopted; which means that, if needed, the analysis may be refined phase by phase. The applicability of the same kind of approach for chemical risk assessment has also been discussed.

5.4 Development of Risk Management Measures (RMMs)

A main element of the CSA involves the descriptions of the RMMs that the users of the substance should apply in order to adequately control the risks. In most cases, the required RMMs are not a single stand-alone tool, but a combination of various control measures. More often they have to be implemented in various combinations, for example, by using technical measures together with instructions and organisational measures.

The exposure estimation performed during the development of ESs refers to the exposures which remain after the implemented/recommended RMM. Therefore, the effectiveness of RMMs should also be known. Also, in order for the RMMs to be effective, the techniques applied should have reliable performance rates.

For the environment, the performance rates of various risk management techniques have been estimated in the BAT Reference Document¹⁶⁵ prepared under the context of IPPC. Thus, this document lists performance rates only for the control measures commonly applied in the chemical sector. For the workplace, various standards exist on the performance of the personal protection measures, however, the actual performance rates of most of the RMMs are very difficult to find. The reference preliminary technical guidance¹⁶⁶ (RIP 3.2-1) provides some protection factors which are based on estimates used in EASE model, and the COSHH Essentials¹⁴⁵ gives some exposure reduction potential estimates in their Control Guidance Sheets. Therefore, there is an urgent need for producing reliable and easily accessible information on the effectiveness of RMMs in various applications.

VTT has excellent facilities and expertise for developing RMMs and detecting their performance for both environmental and occupational risks. VTT's expertise covers, for example, PPE¹⁶⁷⁻¹⁷⁰, safety, health and environment in small process plants¹⁷¹, and accidental releases of chemicals¹⁷²⁻¹⁷³. Studies concerning the performance of technical control measures include modelling the performance of local ventilation systems, the measurement of the performance and identification of the determinants of the performance¹⁷⁴⁻¹⁸³. Also, control measures to various industrial applications (exposure scenarios) have been developed and their efficiency evaluated under actual workplace conditions^{141,184,185}. The performance of various air filters, the determinants of the efficiency, as well as development of novel air filtration systems are also key research topics at VTT^{186,187}.

The concept of the utilisation of, for example, local exhaust ventilation (LEV) is currently very broad. The determinants of exposure used in general ESs include only information on whether LEV are used or not. The utilisation of LEV is assumed to have a universal protection factor, however, because many different types of LEV are available, different protection factors exist, depending on the situation (process/emission source, etc.) where it is used. Therefore, the evaluation of the protection factors of different RMMs in different applications should be performed, and a database of protection factors developed.

VTT should also continue to develop the Kemi-Arvi tool together with the related software companies. A possible direction for further development could be towards better coverage of the emission of the chemicals, and to better account for the determinants of the exposure. The possibilities of combining this tool with the ILO Chemical Control Toolkit¹⁴⁶ should be investigated. Also guidance for the user on the control banding when choosing adequate RMMs could be incorporated. It could also help the user during the risk characterisation phase by determining if the chosen RMM is sufficient to control the associated risks. The possibilities to develop this tool to help the composition of ESs should also be determined.



VTT could participate in research projects exploring the determinants of exposure offering specialised techniques and expertise on, for example, exposure visualisation, the determination of emission rates from materials, etc.

VTT could participate in developing ICT tools for communicating with manufacturers, importers and DUs, or VTT could be an initiator in the development of an RMM performance database. It should take into consideration EU-OSHA's best practises.

6 Socio-Economic Analysis (SEA)

6.1 Development of methodologies for Socio-Economic Analysis

A Socio-Economic Analysis (SEA) is introduced in REACH to examine the social and economic impacts from adopting a particular chemical substance, or restrictions associated with it. A SEA is relevant to two aspects of the REACH proposal^{188A}:

- Industry is invited to submit a SEA (according to Annex XV of the proposal) if it cannot be shown that the risks of a specific substance subject to authorisation are adequately controlled. Under this process, third parties are also invited to submit information on alternatives to the use of the substance subject to authorisation; and
- Member States submitting a restrictions dossier (according to Annex XIV) may also provide a SEA, as may the EChA when preparing a dossier at the request of the Commission. Industry and other stakeholders are invited to submit a SEA (again according to Annex XV), or the input for one, in relation to substances for which restrictions have been proposed.

The preparation of a SEA is relevant to Title VII on Authorisation and Title VIII on the Restrictions on the Manufacturing, Marketing and Use of Certain Dangerous Substances and Preparations. Annex XV outlines the type of information that may be included within a SEA.

The authorisation system is aimed at addressing substances of very high concern, which will then be prioritised by the EChA and may be included in Annex XIII to the REACH proposal. Substances included in Annex XIII shall not be used and placed on the market, unless the use is authorised by the Commission in accordance with a regulatory committee procedure. Authorisations shall be granted for (specific) uses for which the applicant shows that the risks posed by a substance are adequately controlled. Authorisations may be granted where the applicant can demonstrate that the socio-economic benefits for those uses outweigh the risks and there are no suitable alternative substances or technologies. Decisions on granting or refusing authorisations will take into account the opinions of the EChA Committees on risk assessment and on SEA.

Title VIII sets out the proposed procedures for adding or amending restrictions to Annex XVI. A restriction can be any condition for, or prohibition of, the manufacture, use or placing on the market of substances. Such restrictions can be proposed by the Member States or the EChA on behalf of the Commission, with a decision taken on the basis of a regulatory committee procedure. This is to follow the consultation of stakeholders and take into account the opinions of the EChA Committees on risk assessment and on SEA.

Where an applicant cannot demonstrate, or is not confident that he can demonstrate, adequate control of the risks, the applicant may include a SEA into the application for authorisation. The applicant may include an analysis of alternatives covering: risks, technical feasibility and economic feasibility; and where appropriate, the analysis of alternatives should be accompanied by a substitution plan including research and development, and a timetable for actions.

An authorisation shall be granted if the risks are deemed to be adequately controlled. But an authorisation may also be granted if the socio-economic benefits outweigh the risks, and if there are no suitable alternative substances or technologies. An authorisation may, however, be subject to conditions and is normally time limited if based on a SEA.

Annex XV indicates that the level of detail and scope of a SEA is the responsibility of interested parties in relation to an application for an authorisation and proposals for restrictions, and that the SEA may address impacts at any level (company, sector, community).

The types of information that may be included in a SEA are included below^{188A}:

- a) The impacts of a granted or refused authorisation on the applicant (s), or, in the case of a proposed restriction, the impacts on industry (e.g. manufacturers and importers). The impact on all other actors in the supply chain, downstream users and associated businesses in terms of commercial consequences such as impact on investment, research and development, innovation, one-off and operating costs (e.g. compliance; transitional arrangement; changes to existing processes, reporting and monitoring systems; installation of new technology, etc.) taking into account general trends in the market and technology.
- b) The impacts of a granted or refused authorisation, or a proposed restriction, on consumers. For example, products prices, changes in composition or quality or performance of products, availability of products, consumer choice, as well as effects on health and the environment to the extent these affect consumers.
- c) Social implications of a granted or refused authorisation, or a proposed restriction. For example, job security and employment.
- d) Availability, suitability and technical feasibility of alternative substances and/or technologies and economic consequences thereof, and information on the rates of, a potential for, technological change in the sector(s) concerned. In the case of an application for an authorisation, the social and/or economic impacts of using any available alternatives identified in the substitution plan.
- e) Wider implications on trade, competition and economic development (in particular for SMEs and in relation to third countries) of a granted or refused authorisation, or a proposed restriction. This may include consideration of local, regional, national or international aspects.
- f) In the case of a proposed restriction, proposal for other regulatory or non-regulatory measures that could meet the aim of the proposed restriction (this shall take account of existing legislation). This should include an assessment of the effectiveness and the costs linked to alternative RMMs.
- g) In the case of a proposed restriction or refused authorisation, the benefits for health and the environment, as well as the social and economic benefits of the proposed restriction. For example, worker health, environmental performance and the distribution of these benefits, for example, geographically, population groups.
- h) A SEA may also address any other issue that is considered to be relevant by the applicant(s) or interest parties.

The SEA consists of additional information, details and justification on the environmental and human health risks, as well as technical, economic and possible social impacts that are not included in the CSR and that allow the SEA Committee to form its opinion, and the Commission to take a decision. These may include issues like additional health and environmental aspects of alternatives, economic feasibility studies, technical evaluations, and impact analysis on both social and industrial interdependencies.

There are no specific approaches or tools specified for the conduction of the SEA or any parts of it. The REACH Implementation Project 3.9.1^{188B}, provides examples and a discussion on different qualitative and quantitative approaches and their benefits in carrying out a SEA. But there is no common view on the correct ways to fulfil the guidelines of a SEA. Instead, it seems that there is a

need to develop guidelines on how to evaluate the quality of a SEA, and the data and assumptions used for it.

The actors in a SEA include all of the many different stakeholders; like industry and its supply chains and DUs, authorities on the local, regional and national level, and various interest groups and other third parties. There is a need to understand the impacts of the REACH constraints in the different levels of the stakeholder networks.

VTT has an extensive knowledge on most of the issues relevant for a SEA, and many areas of expertise and research needs are presented in the other chapters of this document. VTT can provide its expertise in the additional health and environmental aspects of alternatives, economic feasibility studies, technical evaluations, and impact analysis on both social and industrial interdependencies as well as in knowledge of entire stakeholder-networks, and their formation and functionality under different constraints. For VTT there is a possibility to provide new wider service concepts by unifying several different expertises within a SEA. These service concepts may also include expertise from outside VTT, whenever needed.

The expertise already presented in the earlier chapters can also be used for the subsections of the SEA. These subsections include, for example:

- substitution plans,
- analysis of alternatives including risk analysis and evaluation, and both technical and economic feasibility analysis,
- demonstration of socio-economic benefits by analysing the impacts at the company, aerial, regional and national levels.

There is a need for research to understand the social and economic impacts of REACH at different levels in stakeholder networks, and the impacts of possible alternative actions on the entire network. In the context of REACH, stakeholder networks may include industry and its supply chains and different DUs, and other interest groups that may be affected by the constraints to the production or use of a certain substance. There is also need to evaluate the impacts on the society around the affected industry, from different perspectives. The research on new service concepts for a SEA may be based on VTT's broad knowledge on stakeholder networks and their formation, as well as in their understanding of the risks and vulnerabilities within networks.

6.2 Design and production of substitute chemicals

The chemical industry has dealt with toxicity and pollution issues throughout its entire history, but only recently have they been armed with an understanding of the sources and consequences of these issues. During the 1990s, new ideas and examples of more environmentally friendly chemical processes were introduced, and Paul Anastas coined the term "green chemistry"¹⁸⁹ to focus attention on this rapidly expanding area of research and development. The term green chemistry is defined as "The invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances"¹⁹⁰. While this definition may appear trivial, there are several departures from the traditional chemical design approaches, in which the risk posed by chemical processes have been minimised by limiting exposure in the different stages of handling chemicals:

- a) The concept of design requires the conscious and deliberate use of a set of criteria to create and use chemicals as non-hazardous as possible throughout the entire process. Because of the intentional design, it is also impossible to do green chemistry by accident.

- b) From the phrase "use and generation", it is clear that green chemistry includes all substances that are part of the process, rather than focusing only on those undesirable substances that may be produced in the process.
- c) The definition includes the term "hazardous", as green chemistry deals with risk reduction by addressing the intrinsic hazards of a substance rather than trying to reduce the risks by limiting exposure.

Green chemistry research can be broadly divided into three categories¹⁹¹: alternative feedstocks, alternative solvents, and alternative synthetic pathways. Research related to alternative feedstocks focuses on the use of waste from one process as a feedstock or reagent in another process, or more radically, on the use of renewable or biologically derived sources. Organic solvents are a major source of chemical waste, and research related to alternative solvents tries to find new, more environmentally friendly solvents for the synthesis environment. The most studied alternatives are supercritical fluids^{192,193} and ionic liquids^{193,194}, but in some cases it has been demonstrated that organic reactions can be carried out without using any solvent at all¹⁹⁵. Research related to alternative synthetic pathways is in great part focused on the design of selective catalysts and the design of safer chemicals.

The design of safer chemicals is a process where the chemical structure is analysed in order to identify what parts of the molecule are providing the property desired from the product, and what part is responsible for the unwanted toxicity or hazard. The goal of designing safer chemicals while maintaining the efficacy of function can be achieved through several different strategies, and the choice of strategy is largely dependent on the amount of information that exists on the particular substance¹⁹⁶. If the pathway towards toxicity is known, and if any step within that pathway can be prevented from occurring, then the toxic endpoint can be avoided. This can be achieved by elimination of a toxic functional group or by masking the functional group as a non toxic derivative form and only releasing the parent functionality when necessary. Even if the mechanism of toxic action is unknown, there are still often structure-activity relationships that can be used to design a safer chemical, for example, by altering the length of alkyl side chains. Other approaches for designing safer chemicals include reducing the bioavailability of the substance and replacing persistent chemicals with ones that are designed to degrade after their useful life cycle is over.

The use of more environmental and human health friendly alternative substances and technologies is strongly encouraged in the REACH legislation. In Article 52, aim of authorisation, it is stated that "substances of very high concern are eventually replaced by suitable alternative substances or technologies where these are economically and technologically viable". There are several driving forces for this substitution principle described in the authorisation part of the proposed REACH legislation: For substances of very high concern, information about possible alternative technologies or substances, and the economic and technical feasibility of alternative solutions may be requested from the applicant seeking the authorisation. After the EChA has received all the necessary information about the uses and possibilities regarding the substitution of a chemical, this information will be made available on the EChA's website for a period of time; to allow interested third parties to submit additional information on alternative substances or technologies. An authorisation may be granted for the specific uses of a chemical only if it can be shown that the risks are adequately controlled and there are no suitable alternative substances or technologies. However, this authorisation will be granted for a limited time only, and may be reviewed at any time if new information on possible substitutes becomes available.

In a recent report¹⁹⁷, Greenpeace expressed its concern that the substitution principle is not strongly enough embodied within REACH. They justified their opinion by referring to an OECD report on

Voluntary Approaches for Environmental Policy¹⁹⁸, which is rather strange as there is nothing voluntary about REACH. There is, in fact, a strong need for companies to find substitute chemicals as identifying less hazardous alternatives would make the intensive assessment of the original hazardous chemical unnecessary. Other driving forces for developing less hazardous substitutes include demands from DUs, worker protection, liability issues, increased public awareness, competitive advantage, and company ethics¹⁹⁹. With all these benefits, and also when keeping the possibility for mandatory substitution plans in mind, it is clear that a lot of research focusing on less hazardous substitute chemicals will take place in the EU member states in the following decades. It is also clear that SMEs who cannot afford the same level of research as the large enterprises will need external assistance and guidelines²⁰⁰ on substitution.

VTT has participated in several industrial projects related to the use, design and production of environmentally more acceptable chemicals. One example involved research on alternative corrosion inhibition chemicals applied on district heating pipelines²⁰¹. VTT also has a research team, which has been active in research on inherently safer design of processes.



7 Chemicals under REACH

7.1 Optimisation of the use of hazardous chemicals

The risks of hazardous chemicals usage for typical end users are reasonably well covered by the CSA in the REACH proposal. However, no matter how well the risks are characterised, accidents still do happen. According to "OECD Guiding Principles for Chemical Accident Prevention, Preparedness and Response"²⁰², a chemical accident is defined as "any unplanned event involving hazardous substances, explosions or fires". The main causes for chemical accidents are technological failures and human error, or a combination of both of these. Other causes for chemical accidents involve accidents during the transport of hazardous chemicals²⁰³, natural disasters, and releases due to deliberate action such as sabotage and terrorism.

While the majority of chemical accidents can be attributed to human error, it is still necessary to have human operators controlling process safety because of their inherent flexibility in recovering from abnormal potential accident situations. This flexibility, on the other hand, is the characteristic of human operators that can lead to misjudgements and eventually to accidents. Automation systems can be used to control process safety, but these systems usually fail miserably when something completely unexpected, such as a terrorist attack²⁰⁴, occurs, and therefore human operators will always be required. It may be impossible to exclude all human error, but several ways to reduce both the number of these errors and the impact of them have been presented²⁰⁵. Some of the key considerations that may reduce accidents associated with human error include: achieving a balance between automation and human action, and implementing a well-planned corporate safety policy that includes training related to safety issues, ergonomics of the operator user interface, and inherently safer design.

The concept of inherent safety was first proposed by Kletz²⁰⁶ in 1978. A chemical process can be described as inherently safer if it reduces or eliminates one or more hazards associated with the materials and operations used in the process, when compared to some alternative process, and this reduction or elimination is accomplished by characteristics which are permanent and inseparable parts of the process²⁰⁷. The four basic principles of inherent safety²⁰⁸ are:

- Minimise: Use smaller quantities of hazardous substances.
- Substitute: Replace hazardous substances with less hazardous ones.
- Moderate: Use less hazardous conditions and forms of material.
- Simplify: Design facilities without unnecessary complexity.

Examples on the use of these principles are readily available from the literature^{208,209}.

In a survey²¹⁰ conducted a few years ago, one of the most important reasons for the limited adoption of inherent safety principles was found to be the lack of tried and tested tools for overall process hazard estimation. One of the most comprehensive overall hazard estimation tools, the inherent safety index²¹¹, was developed in Finland. This index is relatively simple and considers both chemical and process safety. The chemical inherent safety index describes the effect of the choice of raw materials and other chemicals on the so-called "inherent safety of the process" through consideration of the heats of reaction, flammability, explosiveness, toxicity, corrosiveness, and incompatibility of chemicals. The process inherent safety index describes the effect of the type of process equipment and process conditions on inherent safety. The parameters considered here include the inventory of chemicals, the process temperature and pressure, the type of processing equipment, and the structure of the process. The separate chemical and process indices are summed

to yield a total inherent safety index. An extension of the inherent safety index based on fuzzy logic has also been presented²¹². The use of the inherent safety index has been extensively demonstrated²¹³⁻²¹⁷ and its performance against other index-based hazard estimation methods has been recently studied²¹⁸. For a review of the inherent safety index and other index-based hazard estimation tools, see the article written by Khan and Amyotte²¹⁹.

The European Council Directive 96/82/EC, commonly also referred to as the "Seveso II" Directive, on the control of major accident hazards involving dangerous substances states that "the presence of dangerous substances shall mean the actual or anticipated presence of such substances in the establishment, or the presence of those *which it is believed may be generated during loss of control of an industrial chemical process*". In a study²²⁰ analysing the major scenarios leading to the unwanted formation of hazardous compounds as a consequence of loss of control of an industrial facility, three main scenarios were identified: fires, runaway reactions, and unwanted reactions. The chemical reactions that may take place during a fire and runaway reactions are difficult to foresee, but an attempt to predict them using artificial intelligence has been presented²²¹. In general, however, this data has to be generated using calorimetric measurements coupled with an appropriate detection system²²²⁻²²⁴. At VTT, there is also a long history of calorimetric measurements associated with hazardous gas detection²²⁵.

7.2 New technology development

New technologies employing the principles of green chemistry, also known as Next Generation Environmental Technologies (NGETs), represent a set of advanced manufacturing technologies that have the potential to produce environmentally benign products and processes. These technologies focus on the redesign of industrial products and processes to reduce the quantity of material inputs and eliminate broad classes of environmentally hazardous outputs rather than focusing on the cleanup and control of waste and hazardous materials. When successfully implemented, NGETs offer the promise of substantial new advances in environmental protection, often at low cost and even with a net economic benefit.

The environmental, economic and safety benefits, as well as the potential barriers for new technology adoption for a wide range of technologies with near-term applications, have been assessed in a recent survey²²⁶ that included 25 case studies. Many of the technologies studied were already in the production stage, and therefore it is not surprising that the benefits obtained with those technologies greatly outweighed any barriers for the technology adoption. In one of the studied cases, however, substantial problems arose: The recycling of polyethylene terephthalate, PET, suffered from unreliable supplies of recyclable material, and the recycling of Nylon was found to be uneconomic because of the price fluctuations of caprolactam, the virgin material for Nylon production. In general, the greatest barriers for new technology adoption identified in the study were as follows:

- *Need for additional research and development:* Companies don't want to invest in technologies that haven't been fully tested in the process scale and might require further research.
- *Need to ensure supply material:* Processes using alternative feedstocks such as by-products or recyclable material may face problems ensuring the supply material availability.
- *Need to make higher starting investments:* Even if the alternative process is proven to be both environmentally and economically superior, the process equipment may require more investments.

- *Need to overcome regulatory barriers:* In case of strict timetables to meet emission limits, the more traditional addition of cleaning systems may be preferred over the development of a truly greener process.

In 1996, a series of working meetings attended by over 200 technical and business leaders from the U.S. chemical industry culminated in the publication of Technology Vision 2020: The U.S. Chemical industry²²⁷. The workshop participants also developed a set of highly ambitious performance-based goals²²⁸ for the U.S. chemical industry to meet by the year 2020:

- Reduce feedstock losses to waste and by-products by 90%,
- Reduce energy intensity by 30%,
- Reduce emissions, including CO₂ and effluents by 30%,
- Increase use of C1 compounds by 20%, and use of renewables by 13%,
- Reduce the time to market through the use of new R&D tools by 30%,
- Increase the number of new products and applications annually by 15%,
- Reduce production costs by 25%.

It is clear that the above ambitious goals cannot be reached by utilising the current so-called new generation environmental techniques (many of which are actually not new at all) alone. For example, extraction with supercritical fluids is usually referred to as a new generation technique, but it has been studied extensively for decades, even at VTT²²⁹⁻²³³. According to the Technology Vision 2020, the most important areas of chemical science that need improvements and new technology development are chemical synthesis, biotechnology and materials technology. Some of the most important needs for these areas of chemistry are outlined in Table 7.

Examples of current VTT research projects related to the development areas listed in Table 7 include, but are not limited to, projects like "New Improvements for Ligno-cellulosic Ethanol (NILE)", "Surface Modification Using Plasma- and Corona Techniques" and "Nanocomposite Polymer Capacitor Films".

The applications of fundamental chemical science depend to a great extent on process science and engineering technology, chemical measurement techniques, and computational technologies. Advances in these areas are needed to transfer the technology created in research laboratories into process-scale operations in an economical and effective way.

The new emerging process chemistries with biochemical and supercritical fluids require the development of reactors with new kinds of hydrodynamic characteristics. Other emerging concepts are associated with the development of integrated reactor and separation systems. In order to cut the R&D times linked to these kinds of systems, advances in computational fluid dynamics (CFD) are needed. Some of the CFD areas that are especially important and need further development include multiphase mixing, reactive flows, non-Newtonian rheology, and dense multiphase turbulent flow. VTT is currently involved in the state-of-the-art research in many of the above areas of CFD computing²³⁴⁻²³⁹.

Process modelling, optimisation and simulation are an integral part of both the development and implementation of the process. However, in most cases our knowledge of particulate processes is incomplete. Advances in accurate on-line measurement techniques in manufacturing environment are needed to provide support for the simulation and analysis of commercial processes with ever increasing complexity. As an example of such a measurement technique, a unique on-line capillary electrophoresis equipment²⁴⁰ is current being developed by VTT. In the process design phase,

thermodynamics simulation tools, such as Chemsheet²⁴¹, can be used to give a deeper understanding of the chemical process studied, and to minimise unnecessary test runs and the amount of waste produced during the testing phase²⁴². Advanced material and energy balance tools²⁴³ can be applied to investigate the economic performance of various process configuration options and to provide support for the process design decision making.

Table 7. The most important needs for the key development areas of chemical science according to US Technology vision 2020.

Development area	Key development needs
Chemical Synthesis	New synthetic techniques with approaches of biology, physics and computational methods. New catalysts and reaction systems. Chemistry for the use of alternative raw materials. Synthesis tools to create multifunctional materials. Techniques for stereospecificity. Chemistry in alternative reaction media.
Biotechnology	Isolation of new enzymes from unexplored microbes. Enhancement of the substrate specificity and activity of known enzymes by molecular biology techniques. DNA sequencing of industrially important micro-organisms and plants. Engineering of sequential enzymatic pathways that perform multiple synthetic steps.
Materials Science	Methods for prediction of material properties. Synthesis technology for precise manipulation of material structures. Enhanced performance in materials. New additive technology to develop routes of step change improvements of material properties. Reuse and disassembly of materials.

8 Downstream user problematics

A Downstream User (DU) is in REACH defined as "any natural or legal person established within the Community, other than the manufacturer or the importer, who uses a substance either on its own or in a preparation, in the course of his industrial or professional activities." The definitions of "Use" and "Undesirable use" are: "any processing, formulation, consumption, storage, keeping, treatment, filling into containers, transfer from one container to another, mixing, production of an article or any other utilisation." and "a use by a downstream user which the registrant (or supplier who prepared a downstream user chemical safety assessment) advises against. Information on undesirable uses is to be given in Section 15 of the safety data sheet. An undesirable use is clearly outside the scope of the supplier exposure scenario." respectively.

One of the aims of REACH is to clarify the division of responsibility for the safe handling of substances along the supply chain. The suppliers of substances have an obligation to provide the new information required under REACH to DUs once registration is complete. After this, they must provide a revised SDS (or other information) with the next delivery of the substance or preparation – at the latest. Within 12 months, the DU must only use the substance in line with the conditions set out in the SDS (or other information).

The DU may need to implement significant changes, if the substance is not registered for the use to which the DU puts it, or there are authorisation conditions or restrictions, which the DU does not meet. It may be difficult for a DU to make these changes within the 12 month period, especially if they need to make changes to the process or to substitute the use of the substance.

It is self-evident that manufacturers and importers only can assess safety based on the available information. It is therefore the responsibility of any actor in the supply chain to forward the relevant information obtained, from downstream or upstream, to the next actor in the chain. In addition, the DU must, for instance, provide feedback in any case where additional information on the substance hazards exists, or where RMMs are regarded to be inappropriate.

8.1 Identification of downstream users and their uses

Manufacturers and importers can only assess the level of safety of the DUs based on the information available to them. If only little information is available, the manufacturer or importer will either assume the "worst case" conditions of use, or not register a use at all, in order to avoid the risk of liability claims.

For many chemicals, there are large numbers of DUs. Following a DU's receipt of the substance or preparation from the supplier (own use and uses further downstream), an ES should be developed for each life-cycle stage. It might therefore be a difficult task to identify all the relevant users and the ways in which the chemical is used. The situation is even more complex if the chemical is used by DUs other than those that are a part of the company's supply chain (such as hired maintenance personnel that come in contact with a chemical in a piece of equipment to be maintained). In addition, SMEs tend to make up the majority of the DUs. And not all these companies are aware of REACH and their duties in its implementation.

The management of supply chains and industrial clusters has, over the years, been the topic of a wide range of studies. Other excellent research projects have been focused on the exposure to chemicals in a variety of industrial sectors. No study that combines these two aspects is, however, known to the authors.

VTT has several research teams that have been involved in different aspects of the management of supply chains. VTT also has knowledge about many industrial branches and about exposure to chemicals.

The process of identifying "real" downstream uses on the one hand, and "worst case" uses on the other, should be studied. There are also "grey areas" concerning exposure that might need to be clarified within a research project. For instance, exposure during the transport of a chemical is excluded from REACH, but, as the truck driver may get exposed to the chemical during loading and unloading the chemical, should the transport company be regarded as a downstream user? Is a maintenance company a downstream user if its personnel are exposed to chemicals present at their customer's premises? Do rescue service workers fall within the scope of REACH?

8.2 The roles of downstream users

As mentioned earlier, the management of supply chains and industrial clusters has, over the years, been the topic of a wide range of studies. It is not known, however, whether any supply chain study related to the roles of DUs as defined by REACH has been carried out, except for those studied by the RIPs.

In REACH, one role of the DUs will be to provide information to the manufacturer or importer. There is currently no requirement, however, to give feedback on, for instance, the quality of the information contained within the SDS, and consequently there is little experience in upstream communication. Under REACH, all DUs (for instance, formulators and end-users of substances and preparations) are required to pass on information up the supply chain. This relates to any new information on the hazardous properties of a substance as such, or contained in a preparation that differs from that obtained in the SDS, or information according to Article 30, and any other information that might call into question the appropriateness of the recommended RMMs.

No research concerning the prerequisites for when a company – as will be required by REACH – is actually willing to send new hazard information up the supply chain (keeping in mind that one result of such information might be that his use may be considered to be an undesirable one), has been found.

In order to prepare ESs for substances or preparations, the DU needs information on how the substance, as such or in a preparation, is used not only by himself but also further downstream, including the:

- processes involved,
- RMMs implemented,
- waste management measures,
- activities of workers, and the duration and frequency of any possible exposure,
- activities of consumers, and the duration and frequency of any possible exposure,
- duration and frequency of emissions.

VTT has the expertise to give DUs guidance on how to determine whether a use is covered by an ES (i.e. where the use is still within the frame of the ES, even though the conditions of use and RMMs differ), or not.

VTT's expertise on supply management can be utilised in studying how information about chemical-related hazards and their prevention can be gathered from the DUs in an efficient way.

8.3 The roles of third parties

REACH associates duties not only to the producers, the importers and the users of the chemicals, but also to third parties, such as distributors (including retailers). These are not defined as "downstream users" but they nevertheless have an obligation to pass information up and down the supply chain.

In many sectors, the distributors also play a relevant role as suppliers, especially of SMEs. This might lead to a communication and cooperation barrier in the supply chain, but then again, it could also enhance the implementation of REACH. Many distributors have a good market overview, and provide consulting and/or technical services for their clients, and thus also know a lot about the actual application of substances and preparations, as well as their properties and functions.

Again, no research has been identified that studies the prerequisites for when a distributor is willing to send new hazard information up the supply chain (keeping in mind that the result of such information might be that the use of the chemical he supplies may be considered to be undesirable and the related business will be lost). For distributors with thousands of customers, the flow of information related to REACH may become a burden and lead to additional costs.

It is still unclear to the authors as to how the general public will be considered under REACH. Depending on the final decisions by the EU, there might still be unresolved issues related to the general public that need to be studied in more detail. Private consumers are not DUs according to REACH and do not have any responsibilities under REACH, but they still need to be considered in the safety assessment for substances on their own, in preparations, or incorporated into articles for consumer use. Where dangerous substances or preparations are offered or sold to the general public, a SDS need not be supplied if sufficient documentation to enable its safe use is provided with the substance/preparation. If consumer use is advised against under Heading 16 of the SDS, or if consumer use is not included in the ES received from supplier, the distributor/retailer is responsible under the General Product Safety Directive (2001/95/EC) for ensuring that it is not sold to the public.

Finally, another category of third parties, e.g. bodies independent of both industry and authorities, might be used as a clearing house for confidential issues.

Being a large research organisation, VTT has established contacts with not only DUs but also with third parties. VTT is also generally considered to be a reliable and neutral partner.

VTT could also take part in studies in selected sectors to evaluate more precisely which information related to REACH (composition, ingredients, uses) should be considered to be confidential, and which should not. Only based on a more comprehensive understanding of the problem, can measures and tools to handle confidentiality be proposed.

8.4 Risk assessment capability

Manufacturers and importers have the right to decide which uses they support, and they are not required to assess and support all identified uses. Consequently, there is a fear that they will not take up uses which are not economically attractive and particularly those which might require additional testing. Therefore, there may be cases where DUs are forced to take over some of the responsibilities from the manufacturers and importers. The CSA is one of these tasks. It requires a certain level of expertise in exposure estimation and risk assessment, as well as resources to organise and carry out the assessment. Terminology and concepts related to chemicals risks in the field of workers health are better known by the DUs than those related to the environment and consumer health. Due to the

implementation of the Chemical Agents Directive (98/24/EC), experience and skills in workplace risk assessment have been gained, and these can be used also in the implementation of REACH. Many DUs do, however, lack even this expertise.

The end-users of chemicals mostly handle preparations in their processes. At present, chemical information focuses on classification and labelling, as well as providing substance-specific information, if required. Formulators are required to merge the information about their input materials (substances and preparations) into a SDS for their preparation.

Due to the current hazard-based system of chemicals regulation, the recommendation of RMMs in SDSs usually does not take account of the actual conditions under which the substance/preparation is applied. The recommendation of RMMs is currently based on the hazards of the substances/preparations, rather than on a risk assessment as required under REACH. This indicates that substance manufacturers and importers, as well as formulators – although being skilled in generic risk assessments – have only limited experience in the assessment of actual risks.

Industrial users have a wide variety of different uses and technologies. The idea of a proposal put forward by the RIP 3.2-1 is that the exposure drivers, or the parameters which are most relevant for the exposure level in a specific use, are described in a quantitative way that provides the calculation parameters needed by the manufacturers and importers for the assessment of safe use. According to RIP 3.2-1, operational conditions of use are described by specifying, amongst others, the substance amounts used per time, and the frequency and duration of substance use. It is not clear, however, that there is a relation between the amount of chemical used per time by a company, and the subsequent risk for exposure.

VTT has experience in risk assessments regarding work places, as well as of the environment, and in compiling information about RMMs. The information about which are the exposure drivers and how they can be quantified is available at the DU level. VTT has the expertise needed to compile the necessary information in a usable way in cooperation with the DUs and/or their organisations. The result of this work would be a description of the operational conditions of use and the RMMs normally applied in the process, including information on the average substance loss from the process, the efficiencies of the RMMs, and the relevant exposure pathways. It is, however, not intended that the actual exposure estimation and risk characterisation is performed for the DU level, and the main task would be to compile information on the operational conditions of use, and the RMMs applied, rather than assessing the exposure levels and the risks a specific substance or groups of substances would pose when used under a particular set of conditions.

Standardised descriptions of conditions of use are widely acknowledged as helpful in limiting the workload and improving the understanding of ESs by DUs. They may also limit the individual communication efforts in the supply chains, as only specific uses may have to be assessed in detail. A proposal of these standardised descriptions must be made on a European level. VTT and other research organisations are believed to have a key role to play in carrying out this task.

8.5 Standardised descriptions of uses

To date, various efforts have been undertaken to assess and narrow down the type of information which needs to be contained in an ES, and the form in which it would be best presented. However, there is currently no broadly accepted agreement on how, and at what level of detail, the information on operational conditions and RMMs should be described in an ES, and various concepts are being discussed.

Based on their knowledge, the DUs of substances and preparations may provide – and should be encouraged to do so – information on the operational conditions of their processes and the RMMs applied to their suppliers. This should preferably be in the form of standardised descriptions of uses for their unit processes, which in some industrial areas also may contain quantifiable information on how the different exposure drivers influence the exposure of humans and the environment. These standardised ESs, which contain descriptions of the conditions of use (operational conditions of use and RMMs) are widely acknowledged as potentially improving the understanding of ESs by both the manufacturers/importers and the DUs.

The work on the standardised descriptions of uses (and the development of generic ESs) is a process relating to the entire supply chain, and should thus not be conducted separately but rather in close international cooperation. The question of how the ESs of preparations are to be consolidated is also relevant to this work.

Standardised descriptions of the use of generic ESs are only of significant use if they are widely accepted – by industry, by the ECHA, as well as the Member State authorities.

Examples of ESs should be developed and tested to get a better and more extensive understanding of their information structure and content. A study should be initiated to assess how the generic ES may be implemented by DUs.

VTT has studied the safe use of chemicals for several decades.

8.6 Understanding new information

When REACH is adopted, DUs of dangerous substances and preparations will receive a SDS, which will look similar to those provided today. In addition, under certain circumstances, these SDSs will have an Annex containing ESs for the identified uses. The ESs are descriptions of how a substance or preparation is to be used safely. It is the DU's obligation to ensure that the way they use a substance, as such or contained in a preparation, is covered by the ESs, and that they implement the respective recommendations for risk management in the SDS. We already know that currently, however, that the DUs are not always making good use of the information in the current SDSs. The authors have been unsuccessful in identifying studies on whether or not this situation is expected to change considerably due to REACH.

Even if the conditions of use (operational conditions of use and RMMs applied) differ from the recommendations in the ES, the use may still be safe and within the framework of REACH. Here, a separate assessment of safety should be carried out. This could, as a first step, involve a simple comparison of whether the differences in conditions of use offset each other. Also a rough screening could be carried out to identify whether, for example, higher efficiencies of RMMs compensate for higher exposure levels.

If no clear decision can be taken on whether or not the use is covered by the ES, a screening level CSA could be performed (see guidance in RIP 3.2). Documenting that the DU has implemented, as a minimum, the conditions in the supplier's ES may include simple calculations, or a re-calculation by use of the information and models used in the supplier's ES.

The ES will indicate which uses are covered and the conditions (and RMMs) under which the use is safe. If the DU's use, for example, "incorporation of substance into articles for consumers" is not

covered by the ES, but the DU implements as a minimum the conditions described in the supplier's ES, a DU CSA is not needed.

Although lacking in both toxicologists and eco-toxicologists, VTT has several researchers that have the experience and the skill to understand the information provided by the manufacturer or importer on the one hand, and to assess the risks involved in a certain use of a chemical on the other. These researchers are also able to compare company-specific situations with those given by the manufacturer or the importer.

The key factor in comparing the risk reduction measures, with those provided in the ES, is their efficiency. That is, the degree of risk reduction at the target achieved by the RMMs, usually shown by a reduced exposure level (e.g. local exhaust ventilation reduces the substance concentration in the workplace air by 50%, gloves reduce dermal exposure by 100%). Normally, it will not be necessary to confirm this by measurement. This may, however, be useful if the DU wishes to demonstrate that his RMMs are at least as efficient as those recommended in the ES. The type of information about efficiency may differ depending on the RMMs applied.

Aside from the obvious possibility for contract research for single companies or single processes, there might also be an opportunity to study how the conditions of use should be reported in the SDSs – in order not only to be clear and helpful, but at the same time neither too detailed nor too general. Another relevant research topic would be to study how well the DUs are able to absorb the information provided, and implement the RMMs described.

8.7 Risk management measures (RMMs)

When REACH is implemented, information on risk management, etc. is to be communicated downstream (recommendations) and upstream (inappropriateness). Whenever the DU's conditions of use (operational conditions, product specification, recommended RMMs) are outside the conditions described in the ES, the DU has four options; they may either:

- shift to another supplier that offers a similar product with an ES that covers the intended use,
- assess whether their operational conditions and RMMs are at least as effective as in the ES, and result in the same (or lower) level of exposure to man and the environment,
- conduct their own assessment, i.e. a so-called DU CSA, and apply for an authorisation,
- improve their RMMs.

If a use has not been authorised, the DU may have to phase out the use of the substance by the "sunset date". This may require changes to complex processes and products, with potential impacts on product quality where ready substitutes are not available. In some sectors, substitution and exchange of substances could (due to non-REACH requirements) require re-qualification of products and/or processes. In these sectors, the fear of substance withdrawal and the resulting losses of essential substances and preparations for the process is high.

Also, the likelihood that DUs have to allocate significant resources for assessing whether they operate in agreement with the conditions of use communicated by the supplier(s) increases with the level of detail of the ESs they receive. The broader the ES (less specific requirements), the more expertise is needed by DUs to check whether they are covered or not. Different wordings used by different suppliers of the same chemical may confuse the DUs even further.

Types of on-site RMMs include technical exposure controls (e.g. LEV, incineration of exhaust gases), PPE (gloves, goggles, etc.) and process integrated measures. The off-site RMMs usually address sewage treatment plants, waste collection and treatment, as well as product-related measures.

If a RMM (on site or off-site) works in a similar way to that described in the ES, the comparison of efficiencies is fairly straightforward. If the process and the associated RMMs are designed in a different way, the comparison of efficiencies is more complicated and requires some level of assessment or calculation. A pragmatic approach could be to document efficiency by monitoring data or modelling of emission or exposure levels (which may already be available, or may be needed to document compliance with other legislation).

A vast amount of resources have been invested in research in order to improve processes and work conditions and to reduce emissions to the environment, and it is self-evident that it is impossible to include a review of the state-of-the-art of all these fields in this Discussion Paper

As a consequence of the implementation of REACH, the need for new RMMs will increase in Europe. It is, however, not yet clear as to which uses will be undesirable, or which chemicals will not be available for use within the EU, and thus need to be substituted. A process for the identification of potential research needs should be started as soon as possible.

VTT has vast experience in both the development of processes and in chemical safety, for example, in identifying exposure to chemicals, and in searching for solutions to reduce the exposure.

For instance, in order to detect exposure patterns during moulding operations, worker's styrene exposure was determined using the Finnish Picture Mixed Exposure method FINN-PIMEX, which combines continuous exposure measurements and video recording. From this data, a task-specific exposure analysis can be performed.

In addition, VTT is one of the organisations that has also investigated inherently safer process alternatives. Also, the EU sponsored project SPASE, which was led by VTT, included a workpackage in which instructions for a variety of risk reduction measures were generated. VTT also has several teams of experts developing new or improved processes for industry.

8.8 Downstream Users' internal IT-tools

REACH poses challenges also to the internal organisation of enterprises. The information and competences related to the use of substances used by the DUs may be scattered throughout the company. The technical specialists may know details concerning the process conditions, while the environmental managers may know details about the input materials, and labour safety managers may know information concerning the exposure levels of the workers. The sales department may have the best knowledge about what the customers do with their own products, and the purchasing department may be the only one having direct contact with the suppliers. Compliance with REACH will therefore require increased company-internal cooperation, as the knowledge on substances and preparations has to be brought together.

As shown above, communication triggered by the need to comply with REACH may relate to different issues and thus there may be a need to address many different persons within an enterprise. At the moment, no clear responsibilities seem to be assigned for these aspects in enterprises, and in particular, not in SMEs. This may hinder not only internal communication, but also communication along the supply chain, as it is not clear about who to address.



A software tool comparable to similar tools used for other purposes by, for instance, the pharmaceutical industry, is expected to be needed in order to handle internal REACH communication. Also, most enterprises are currently forced to manually enter the information from a SDS into their material management systems. It may be a good and resource saving idea to implement the SDSs and related ESs in an electronic, computer readable form, which is compatible with other widely used computer programs.

Presently, a number of commercially available IT tools for SDS management have been developed and are in use by many enterprises. These programmes may present a suitable platform for developing more versatile software that will cover all the needs that REACH will raise within the DU companies. Although it is not a software house, VTT has several researchers that are involved in the development of IT-tools (contents, specifications, programming, etc.). The programming of such a tool, however, would probably need to be carried out by a software company.

A study is needed in order to provide guidance on how the compliance may be documented using the current available systems, as far as possible. The result of the study might also be that there is a need for a "REACH Master File" for each chemical or formulation for which the DU is responsible. Suggestions on the content of such a file would, however, need to be the result of an international study.

8.9 REACH vs. other legislation relevant to the downstream user

Requirements from environmental and workers protection legislation will remain in place even when REACH is implemented. It is therefore important to clarify and communicate that the responsibility for the safety of workers remains with their direct employers, that the responsibility for installation-related and/or environmental legislation remains with the operators of such installations, and that the responsibility for safe products remains with those who place them on the market. REACH, by generating information on substance properties and safe uses may facilitate compliance with other legal requirements.

Again, no research results on this topic have been found in the open literature.

VTT have researchers that are familiar with most of the relevant legislation currently in place within the EU. VTT has, for instance, investigated and reported on the implementation of the major hazards directive (Seveso II Directive). This expertise can be utilised in possible research projects on the topics mentioned above.

This topic is more a question of education and less about research. It is, however, important to consider also other relevant legislation whenever research regarding DUs is carried out.

9 Conclusions

The purpose of this paper is to highlight the possibilities that are raised by the European new chemical legislation known as REACH.

The fundamental ideology of the REACH system is to collect the best available physico-chemical, toxicological and ecotoxicological information regarding hazardous chemicals, and then also control their usage in order to minimise the risks on humans and environment.

REACH is a driver for innovation and it will create direct and indirect research needs in the future.

Particularly interesting research fields include the development of:

- calculation methods for selected physico-chemical parameters, such as n-octanol/water coefficient, flash point and vapour pressure,
- ecotoxicological testing methods, such as absorption, chemical leaching, bioavailability and biodegradability of organic pollutants in different environmental conditions (and paying specific attention to northern conditions),
- *In vitro* test and fast screening methods, for example, by means of cell-based screening (GE) for making it easier to focus the testing on compounds that have toxic profiles, and lowering the threshold for industry to design new formulations,
- *In silico* methods, such as QSARs,
- exposure scenario approaches, tools and implementation for humans and the environment,
- environmental risk assessment; taking account of life-cycle assessment of processes and products, emissions to air, mobility studies and transport models,
- socio-economic analysis tools and implementation; developing methodology for analysing technical feasibility, cost and health effects of alternatives,
- substitute chemicals, and new environmentally benign technologies,
- systematic tools and methods for the implementation of REACH, e.g. clarifying DU problematics.

It is our responsibility to the next generations to develop new tools, techniques and methods to ensure that this goal is achieved.

References

1. OECD Series On Testing And Assessment. *1. Guidance Document For The Development Of OECD Guidelines For The Testing Of Chemicals*, Environment Directorate, OECD, Paris 2006.
2. *The EU Testing Methods Adoption Process*, European Chemicals Bureau, Ispra 2005
http://ecb.jrc.it/DOCUMENTS/Testing-Methods/TM_procedure_March_2005.pdf (Accessed 28.11.2006)
3. *Official Journal of the European Union* **L 383 A** (1992).
4. *Official Journal of the European Union* **L 305** (1998).
5. *Official Journal of the European Union* **L 152** (2004).
6. Marino, D.J. Variability in physical constant parameter values from standard data sources and the implication of this variability for risk analysis, *Risk Analysis* **26** (2006) pp.185-201.
7. OECD Guidelines For The Testing Of Chemicals. *Proposal For Updating Guideline 104. Vapour Pressure*, OECD, Paris 2002.
8. *Guidance Document on the Determination of Particle Size Distribution, Fibre Length and Diameter Distribution of Chemical Substances*, DRAFT version of document EUR 20268 EN (2002), European Chemicals Bureau, Ispra, 18 p.
9. OECD Testing Guideline 110: *Particle Size Distribution/ Fibre Length and Diameter Distribution*, OECD, Paris, 1983.
10. OECD Guidelines For The Testing Of Chemicals. *Proposal For A New Guideline. 123. Partition Co-efficient (1-Octanol/Water): Slow-Stirring Method*, OECD, Paris 2003.
11. OECD Guidelines For The Testing Of Chemicals. *Proposal For A New Guideline. 122. Partition Coefficient (n-Octanol/Water) pH-Metric Method for Ionisable Substances*, OECD, Paris 2000.
12. Kong, X.Q, Shea D., Gebreyes, W.A. and Xia, X.-R., Novel hydrophobicity ruler approach for determining the octanol/water partition coefficients of very hydrophobic compounds via their polymer/solvent solution distribution coefficients, *Anal. Chem.* **77** (2005) pp.1275-1281.
13. Donovan, S.F. and Pescatore, M.C., Method for measuring the logarithm of octanol-water partition coefficient by using short octadecyl-poly(vinyl alcohol) high-performance liquid chromatography columns, *J. Chromatogr. A* **952** (2002) pp.47-61.
14. Mazzobre, M.F., Román, M.V. Mourelle, A.F. and Corti, H.R., Octanol-water partition coefficient of glucose, sucrose, and trehalose, *Carbohydr. Res.* **340** (2005) pp.1207-1211.
15. Brooke, D.N., Dobbs, A.J. and Williams, N., Octanol/water partition coefficients (P): Measurement, estimation, and interpretation, particularly for chemicals with $P > 10^5$. *Exotoxicol. Environ. Safety*, **11** (1986) pp.251-260.
16. Tolls, J., Bodo, K., De Felip, E., Dujardin, R., Hwa Kim, Y., Moeller-Jensen, L., Mullee, D., Nakajima, A., Paschke, A., Pawliczek, J.-B., Schneider, J., Tadeo, J.-L., Tognucci, A.C., Webb, J. and Corneel Zwijzen, A., Slow-Stirring Method For Determining The n-Octanol/Water Partition Coefficient (Pow) For Highly Hydrophobic Chemicals: Performance Evaluation In A Ring Test, *Environ. Toxicol. Chem.*, **22** (2003) pp.1051-1057.
17. Takács-Novák, K. and Avdeef, A., Interlaboratory study of logP determination by shake-flask and potentiometric methods, *J. Pharmaceut. Biomed. Anal.*, **14** (1996) pp.1405-1413.
18. Slater, B., McCormack, A., Avdeef, A. and Comer, J.E., pH-metric logP. 4. Comparison of partition coefficients determined by HPLC and potentiometric methods to literature values, *J. Pharm. Sci.*, **83** (1994) pp.1280-1283.
19. Avdeef, A., Berger, C.M. and Brownell, C., pH-metric solubility. 2: Correlation between the acid-base titration and the saturation shake-flask solubility-pH methods, *Pharmaceut. Res.*, **17** (2000) pp.85-89.
20. Woodburn, K.B., Doucette, W.J. and Andren, A.W., Generator column determination of octanol/water partition coefficients for selected polychlorinated biphenyl congeners, *Environ. Sci. Technol.*, **18** (1984) pp.457-459.
21. Ishihama, Y., Oda, Y., Uchikawa, K. and Asakawa, N., Evaluation of solute hydrophobicity by microemulsion electrokinetic chromatography, *Anal. Chem.*, **67** (1995) pp.1588-1595.
22. Razak, J.L., Cutak, B.J., Larive, C.K. and Lunte, C.K., Correlation of the capacity factor in vesicular electrokinetic chromatography with the octanol:water partition coefficient for charged and neutral analytes, *Pharm. Res.*, **18** (2001) pp.104-111.
23. Zhongjiang, J., Physicochemical profiling by capillary electrophoresis, *Curr. Pharmaceut. Anal.*, **1** (2005) pp.41-56.
24. Arthur, C.L., Pratt, D., Motlaph, S., Pawliszyn, J. and Belardi, R., Environmental analysis of organic compounds in water using solid phase micro extraction, *J. High Resolut. Chromatogr.* **15** (1992) p.741.
25. Poerschmann, J., Gorecki, T. and Kopinke, F.D., Sorption of very hydrophobic organic compounds onto poly(dimethylsiloxane) and dissolved humic organic matter. 1. Adsorption or partitioning of VHOC on PDMS-coated solid-phase microextraction fibers - A never-ending story?, *Environ. Sci. Technol.*, **34** (2000) pp.3824-3830.

26. El Tayar, N., Tsai, R.-S., Carrupt, P.-A. and Testa, B., Octan-1-ol-water partition coefficients of zwitterionic amino acids. Determination by centrifugal partition chromatography and factorisation into steric/hydrophobic and polar components, *J. Chem. Soc. Perkin Trans.*, **2** (1992) pp.79-84.
27. Caron, G., Steyaert, G., Pagliara, A., Reymond, F., Crivori, P., Gaillard, P., Carrupt, P.-A., Avdeef, A., Comer, J., Box, K.J., Girault, H.H. and Testa, B., Structure-lipophilicity relationships of neutral and protonated blockers, part I: intra and intermolecular effects in isotropic solvent systems, *Helv. Chim. Acta.*, **82** (1999) pp.1211-1222.
28. Bouchard, G., Pagliara, A., van Balen, G., Carrupt, P.-A., Testa, B., Gobry, V., Girault, H.H., Caron, G., Ermondi, G. and Fruttero, R., Ionic partition diagram of the zwitterionic antihistamine cetirizine, *Helv. Chim. Acta.*, **84** (2001) pp.375-387.
29. Gluck, S.J., Determination of octanol/water partition coefficients by flow injection analysis, *Anal. Chim. Acta*, **214** (1988) pp.315-327.
30. Danielsson, L.-G. and Zhang, Y.-H., Mechanised determination of n-octanol/water partition constants using liquid-liquid segmented flow extraction, *J. Pharm. Biomed. Anal.*, **12** (1994) pp.1475-1481.
31. Danielsson, L.-G. and Zhang, Y.-H., Methods for determining n-octanol-water partition constants, *Trends Anal. Chem.*, **15** (1996) pp.188-196.
32. Fujita, T., Iwasa, J. and Hansch, C., A new substituent constant, π , derived from partition coefficients, *J. Am. Chem. Soc.*, **86** (1964) pp.5175-5180.
33. Rekker, R.F., *The hydrophobic fragmental constant*, Pharmacochemistry Library, Elsevier, New York, 1977, Vol.1.
34. Hansch, C. and Leo, A.J., *Substituent constants for correlation analysis in chemistry and biology*, John Wiley, New York, 1979.
35. Marrero, J. and Gani, R., Group-contribution-based estimation of octanol/water partition coefficient and aqueous solubility, *Ind. Eng. Chem. Res.*, **41** (2002), pp.6623-6633.
36. Livingstone, D.J., Ford, M.G., Huuskonen, J.J. and Salt, D.W., Simultaneous prediction of aqueous solubility and octanol/water partition coefficient based on descriptors derived from molecular structure, *J. Comput.-Aided Mol. Design*, **15** (2001) pp.741-752.
37. Huuskonen, J.J., Villa, A.E.P. and Tetko, I., Prediction of partition coefficient based on atom-type electrotopological state indices, *J. Pharm. Sci.*, **88** (1999) pp.229-233.
38. Wang, R., Gao, Y. and Lai, L., Calculating partition coefficient by atom-additive method, *Pers. Drug Discovery Design*, **19** (2000) pp.47-66.
39. Klopman, G., Li, J.-Y., Wang, S. and Dimayga, M., Computer automated log P calculations based on an extended group contribution approach, *J. Chem. Inf. Comp. Sci.*, **34** (1994) pp.752-781.
40. Meylan, W.M. and Howard, P.H., Atom/fragment contribution method for estimating octanol-water partition coefficients, *J. Pharm. Sci.*, **84** (1995) pp.83-92.
41. Mannhold, R. and Dross, K., Calculation procedures for molecular lipophilicity: A comparative study, *Quant. Struct.-Act. Relat.*, **15** (1996) p.403.
42. Kamlet, H.J., Doherty, R.M., Abraham, M.H., Marcus, Y. and Taft, R.W., Linear solvation energy relationships. 46. An improved equation for correlation and prediction of octanol/water partition coefficients of organic nonelectrolytes (Including strong hydrogen bond donor solutes), *J. Phys. Chem.*, **92** (1988) pp.5244-5255.
43. Abraham, M.H., Chadha, H.S., Whiting, G.S. and Mitchell, R.C., Hydrogen bonding. 32. An analysis of water-octanol and water-alkane partitioning and the delta log P parameter of seiler, *J. Pharm. Sci.*, **83** (1994) pp.1085-1100.
44. Goss, K.-U. and Schwarzenbach, R.P., Linear free energy relationships used to evaluate equilibrium partitioning of organic compounds, *Environ. Sci. Technol.*, **35** (2001) pp.913-924.
45. Chiou, C.T., Schmedding, D.W. and Manes, M., Improved prediction of octanol-water partition coefficients from liquid-solute water solubilities and molar volumes, *Environ. Sci. Technol.*, **39** (2005) pp.8840-8846.
46. Torrens, F., Sánchez-Marín, J. and Nebot-Gil, I., Universal model for the calculation of all organic solvent-water partition coefficients, *J. Chromatogr. A*, **827** (1998) pp.345-358.
47. Curutchet, C., Orozco, M. and Lague, F.J., Solvation in octanol: Parametrisation of the continuum MST model, *J. Comput. Chem.*, **22** (2001) pp.1180-1193.
48. Breindl, A., Beck, B., Clark, T. and Glen, R.C., Prediction of the octanol/water partition coefficient, log P, using a combination of semiempirical MO-calculations and a neural network, *J. Mol. Model.*, **3** (1997) pp.142-155.
49. Aliste, M.P. and Tieleman, P.D., Computer simulation of partitioning of ten pentapeptides Ace-WLXLL at the cyclohexane/water and phospholipid/water interfaces, *BMC Biochemistry*, **6**:30 (2005)
50. Renner, R., The K_{ow} controversy, *Environ. Sci. Technol.*, **36** (2002) A411-A412.
51. Catoire, L., Paulmier, S. and Naudet, V., Experimental determination and estimation of closed cup flash points of mixtures of flammable solvents, *Process Safety Prog.*, **25** (2006) pp.33-39.
52. Butler, R.M., Cooke, G.M., Lukk, G.G. and Jameson, B.G., Prediction of flash points of middle distillates, *Ind. Eng. Chem.*, **48** (1956) p.808.
53. Prugh, R.W., Estimation of flash point temperature, *J. Chem. Educ.*, **50** (1973) A85-A89.

54. Patil, G.S., Estimation of flash point, *Fire Materials*, **12** (1987) pp.127-131.
55. Satyanarayana, K. and Kakati, M.C., Note: Correlation of flash points, *Fire Materials*, **15** (1991) pp.97-100.
56. Metcalfe, E. and Metcalfe, A.E.M., Communication: On the correlation of flash points, *Fire Materials*, **16** (1992) pp.153-154.
57. Satyanarayana, K. and Rao, P.G., Improved equation to estimate flash points of organic compounds, *J. Hazard. Mater.*, **32** (1992) pp.81-85.
58. Hshieh, F.-Y., Correlations of closed-cup flash points with normal boiling points for silicone and general organic compounds, *Fire Materials*, **21** (1997) pp.277-282.
59. Catoire, L. and Naudet, V., A unique equation to estimate flash points of selected pure liquids. Application to the correction of probably erroneous flash point values, *J. Phys. Chem. Ref. Data*, **33** (2004) pp.1083-1111.
60. Katritzky, A.R., Petrukhin, R., Jain, R. and Karelson, M., QSPR analysis of flash points, *J. Chem. Inf. Comput. Sci.*, **41** (2001) pp.1521-1530.
61. Tetteh, J., Suzuki, T., Metcalfe, E. and Howells, S., Quantitative structure-property relationships for the estimation of boiling point and flash point using a radial basis function neural network, *J. Chem. Inf. Comput. Sci.*, **39** (1999) pp.491-507.
62. Suzuki, T., Ohtaguchi, K. and Koide, K., A method for estimating flash points of organic compounds from molecular structures, *J. Chem. Eng. Jpn.*, **24** (1991) pp.258-261.
63. Albahri, T.A., Flammability characteristics of pure hydrocarbons, *Chem. Eng. Sci.*, **58** (2003) pp.3629-3641.
64. CHETAH 8.0, The computer program for chemical thermodynamics and energy release evaluation, ASTM International, 2006.
<http://www.southalabama.edu/engineering/chemical/chetah/> (Accessed 28.11.2006)
65. Cranium 1.0.3, Property estimation software, *Molecular Knowledge Systems Inc.*, 2006.
<http://www.molknow.com/> (Accessed 28.11.2006)
66. Superchems 5.91, Software for pressure relief design, chemical reactivity assessment and management, consequence analysis, and quantitative risk analysis, *ioMosaic Corporation*, 2006.
<http://www.iomosaic.com/iomosaic/products/software/SuperChems.html> (Accessed 28.11.2006)
67. Montemayor, R.G., Collier, M.A. and Lazarczyk, G.G., Precision and equivalence of automatic and manual flash point apparatus, *J. Testing Evaluation*, **30** (2002) pp.74-84.
68. Montemayor, R.G., The effect of kinematic viscosity on the flash point of liquids determined by ASTM D 93 procedure A, ASTM D 93 procedure B, and ASTM D 56, *J. Testing Evaluation*, **27** (1999) pp.388-395.
<http://www.chemsheet.com/> (Accessed 28.11.2006)
69. *Technical Guidance Document on Risk Assessment. Part 1., 2. Ed.*, European Commission, Joint Research Centre, Ispra, Italy 2003, EUR 20492 EN/1, 303 p.
71. Winder, C., Azzi, R. and Wagner, D., The development of the globally harmonized system (GHS) of classification and labeling of hazardous chemicals, *J. Haz. Mat.*, **A125** (2005) pp.29-44.
72. Itävaara, M. and Vikman, M., A simple screening test for studying the biodegradability of insoluble polymers, *Chemosphere*, **31** (1995) pp.4359-4373.
73. Itävaara, M., Karjomaa, S. and Selin, J.-F., Aerobic and anaerobic biodegradation of PLLA at thermophilic conditions, *Chemosphere*, **46** (2002) pp.879-885.
74. Itävaara, M., Piskonen, R. and Rytönen, J., Biodegradation of crude oil in cold climate conditions. In: *Bioremediation of Contaminated Soils*, 2nd Edition. Eds. Wise, D.L. *et al.*, Marcel Dekker Inc. 270 Madison Avenue, New York, NY 2002, pp.327-337.
75. Itävaara, M. and Vikman, M., An overview of methods for biodegradability testing of biopolymers and packaging materials, *Journal of Environmental Polymer Degradation*, **4** (1996) pp.29-36.
76. Piskonen R., Kapanen A., Mansikka T., Rytönen J., and Itävaara M., Evaluation of bioremediation in a shoreline-simulating microcosm, *Bioremediation Journal*, **6** (2002) pp.143-158.
77. Tuominen, J., Kylmä, J., Kapanen, A., Venelampi, O., Itävaara M., and Seppälä, J., Biodegradation of lactic acid based polymers under controlled composting conditions and evaluation of the ecotoxicological impact, *Biomacromolecules*, **3** (2002) pp.445-455.
78. Nyssönen, M., Piskonen, R., and Itävaara, M., A targeted quantitative real-time PCR assay for studying naphthalene degradation in the environment, *Microbial Ecology*, submitted, Accepted after revision, in press.
79. Piskonen, R., Nyssönen, M., Rajamäki, T. and Itävaara, M., Monitoring of accelerated naphthalene-biodegradation in a bioaugmented soil slurry, *Biodegradation*, **16** (2004) pp.127-134.
80. Piskonen, R., Nyssönen, M., Rajamäki, T., and Itävaara, M., Evaluation of chemical pretreatment of contaminated soil for improved PAH bioremediation, *Appl. Microbiology and Biotechnology*, **65** (2004) pp.627-634.
81. Kapanen, A. and Itävaara, M., REVIEW Ecotoxicity Tests for Compost Applications, *Ecotoxicology and Environmental Safety*, **49B** (2001) pp.1-16.

82. Degli-Innocenti, F. Bellia, G., Tosin, M., Kapanen, A. and Itävaara, M., Detection of toxicity released by biodegradable plastics after composting in activated vermiculite, *Polymer Degradation and Stability*, **73** (2001) pp.101-106.
83. Novotny, Č, Dias, N., Kapanen, A., Malachová, K., Vandrovčova, M., Itävaara, M., and Lima, N., Comparative use of bacterial, algal and protozoan tests to study toxicity of azo-and antraquinone dyes, *Chemosphere*, **63** (2006) pp.1236-1442.
84. TAPIR. Three point three – A Project for the Information Requirements of REACH, Final report submitted to European Chemical Bureau, Joint Research Centre, European Commission, Cefic, DK-EPA, Environment Agency of England and Wales, ECETOC, INERIS, KemI and TNO, 2005, 76 p.
85. Landis, G.W., and Yu, M-H., *Introduction to Environmental Toxicology: Impacts of Chemicals Upon Ecological Systems*, CRC Press (Lewis), Boca Raton, FL 1995, 328 p.
86. <http://ecvam.jrc.it/> (Accessed 28.11.2006)
87. <http://www.uta.fi/jarjestot/fincopa/vaihtoehto.htm> (Accessed 28.11.2006)
88. Selassie, C.D., *History of quantitative structure-activity relationships*, in Burger's Medicinal Chemistry and Drug Discovery, 6. Ed., Vol.1: Drug Discovery, Edited by Abraham, D.J., John Wiley & Sons Inc. (2003), pp. 1-47.
89. Hansch, C., Maloney, P.P., Fujita, T. and Muir, R.M., Correlation of biological activity of phenoxyacetic acids with Hammett substituent constants and partition coefficients, *Nature*, 194 (1962) pp.178-180.
90. Hansch, C. and Fujita, T., ρ - σ - π analysis. A method for the correlation of biological activity and chemical structure, *J. Am. Chem. Soc.*, **86** (1964) pp.1616-1626.
91. Taft, R.W., Polar and steric substituent constants for aliphatic and o-benzoate groups from rates of esterification and hydrolysis of esters, *J. Am. Chem. Soc.*, **74** (1952) pp.3120-3128.
92. Schultz, T.W., Cronin, M.T.D., Walker, J.D., and Aptula, A.O., Quantitative structure-activity relationships (QSARs) in toxicology: A historical perspective, *J. Mol. Struct. THEOCHEM*, **622** (2003) pp.1-22.
93. Hansch, C., Hoekman, D. and Gao, H., Comparative QSAR: Toward a deeper understanding of chemicobiological interactions, *Chem. Rev.*, **96** (1996) pp.1045-1075.
94. Multicase Inc., Beachwood, OH.
<http://www.multicase.com/> (Accessed 28.11.2006)
95. Accelrys Inc., Cambridge, UK.
<http://www.accelrys.com/products/topkat/> (Accessed 28.11.2006)
96. Optimised approach based on structural indices set (OASIS), Prof. Assen Zlatarov University, Bourgas, Bulgaria.
97. Jaworska, J., Dimitrov, S., Nikolova, N. and Mekenyan, O., Probabilistic assessment of biodegradability based on metabolic pathways: CATABOL system, *SAR QSAR Environ. Res.*, **13** (2002) pp.307-323.
98. Eriksson, L., Jaworska, J., Worth, A.P., Cronin, M.T.D. and McDowell, R.M., Methods for reliability and uncertainty assessment and for applicability evaluations of classification- and regression-based QSARs, *Environ. Health Perspect.*, **111** (2003) pp.1361-1375.
99. Pedersen, F., de Bruhin, J., Munn, S. and van Leeuwen, K., Assessment of additional testing needs under REACH. Effect of (Q)SARs, risk based testing and voluntary industry initiatives, European Commission, Joint Research Centre, Institute for Health and Consumer Protection, Ispra, Italy 2003, 36 p.
100. Cronin, M.T.D., Walker, J.D., Jaworska, J.S., Comber, M.H.I., Watts, C.D. and Worth, A.P., Use of QSARs in international decision-making frameworks to predict ecological effects and environmental fate of chemical substances, *Environ. Health Perspect.*, **111** (2003) pp.1376-1390.
101. Cronin, M.T.D., Jaworska, J.S., Walker, J.D., Comber, M.H.I., Watts, C.D. and Worth, A.P., Use of QSARs in international decision-making frameworks to predict health effects of chemical substances, *Environ. Health Perspect.*, **111** (2003) pp.1391-1401.
102. Jaworska, J.S., Comber, M., Auer, C. and van Leeuwen, C.J., Summary of a workshop on regulatory acceptance of (Q)SARs for human health and environmental endpoint, *Environ. Health Perspect.*, **111** (2003) pp.1358-1360.
103. Anon., OECD series on testing and assessment. 49. The report from the expert group on (quantitative) structure-activity relationships [(Q)SARs] on the principles for the validation of (Q)SARs., OECD (2004), 206 p.
104. Worth, A.P., Bassan, A., Gallegos, A., Netzeva, T.I., Patlewicz, G., Pavan, M., Tsakovska, I. and Vracko, M., The characterisation of (quantitative structure-activity relationships: Preliminary guidance, EUR 21866 EN, European Chemicals Bureau, Institute for Health and Consumer Protection, Italy 2005, 95 p.
105. Netzeva, T.I., Worth, A.P., Aldenberg, T., Benigni, R., Cronin, M.T.D., Gramatica, P., Jaworska, J.S., Kahn, S., Klopman, G., Marchant, C.A., Myatt, G., Nikolova-Jeliazkova, N., Patlewicz, G.Y., Perkins, R., Roberts, D.W., Schulz, T.W., Stanton, D.T., van de Sandt, J.J.M., Tong, W., Veith, G. and Yang, C., Current status of methods for defining the applicability domain of (quantitative) structure-activity relationships. The report and recommendations of ECVAM workshop 52, *ATLA*, **33** (2005) pp.1-19.
106. Cramer III, R.D., Bunce, J.D., Patterson, D.E. and Frank, I.E., Cross validation, bootstrapping and partial least squares compared with multiple regression in conventional QSAR studies, *Quant. Struct.-Act. Relat.*, **7** (1988) pp.18-25.
107. Cronin, M.T.D. and Shulz, T.W., Pitfalls in QSAR, *J. Mol. Struct. THEOCHEM*, **622** (2003) pp.39-51.

108. Livingstone, D.J., The characterisation of chemical structures using molecular properties. A survey, *J. Chem. Inf. Comput. Sci.*, **40** (2000) pp.195-209.
109. Karelson, M. and Lobanov, V.S., Quantum-chemical descriptors in QSAR/QSPR studies, *Chem. Rev.*, **96** (1996) pp.1027-1043.
110. ECOSAR: A Computer Program for Estimating the Ecotoxicity of Industrial Chemicals, and Estimating Toxicity of Industrial Chemicals to Aquatic Organisms Using Structure Activity Relationships, U.S. EPA 2006. <http://www.epa.gov/oppt/newchems/tools/21ecosar.htm> (Accessed 28.11.2006)
111. Derek for Windows, Lhasa Ltd, Leeds, UK, 2006. <http://www.lhasalimited.org/> (Accessed 28.11.2006)
112. Biodegradation Database and Estimation, Japanese Chemicals Evaluation and Research Institute, Tokyo 2006. <http://qsar.cerij.or.jp/cgi-bin/QSAR/index.cgi?e> (Accessed 28.11.2006)
113. *Technical Guidance Document on Risk Assessment. Part 3*, 2. Ed., European Commission, Joint Research Centre, Ispra, Italy 2003, EUR 20492 EN/3, 104 p.
114. Anon., Report on the Regulatory Uses and Applications in OECD Member Countries of (Quantitative) Structure-Activity Relationship [(Q)SAR] Models in the Assessment of New and Existing Chemicals, OECD Draft of September 2005, 55 p.
115. European Chemicals Bureau Newsletter, 2005 (4), December 23, 2005, p.10.
116. Pavan, M., Worth, A.P. and Netzeva, T.I., Preliminary analysis of aquatic toxicity dataset and assessment of QSAR models for narcosis, EUR 21749 EN, European Chemicals Bureau, Ispra, Italy 2005, 158 p.
117. Pavan, M., Worth, A.P. and Netzeva, T.I., Comparative assessment of QSAR models for aquatic toxicity, EUR 21750 EN, European Chemicals Bureau, Ispra, Italy, 2005, 111 p.
118. Tsakovska, I., Netzeva, T. and Worth, A., Evaluation of (Q)SARs for the prediction of eye irritation/corrosion potential. Physicochemical exclusion rules, EUR 21897 EN, European Chemicals Bureau, Ispra, Italy, 2005, 38 p.
119. Rojire, E. and Hulzebos, E., Evaluation of (Q)SARs for the prediction of skin irritation/corrosion potential, National Institute of Public Health, Bilthoven, Netherlands, 2005, 45 p.
120. Bassan, A., Development of Computational (Q)SAR Tools useful for REACH Implementation, presentation held at QSAR 2006, Lyon, France, 8-12 May 2006. http://ecb.jrc.it/DOCUMENTS/QSAR/INFORMATION_SOURCES/PRESENTATIONS/Bassan_Lyon_0605.pdf (Accessed 28.11.2006)
121. Gini, G., Scoping Study for the Development of an Internet Based Decision Support System for (Quantitative) Structure Activity Relationships, Final Report for JRC, Polytechnico di Milano, Italy, 13 May 2005.
122. Danish (Q)SAR Database, internet version published by JRC 2005. <http://ecbqsar.jrc.it/> (Accessed 28.11.2006)
123. Bassan, A. and Patlewicz, G., User Manual for the Internet Based Version of the Danish (Q)SAR Database, Database version 1, May 2005, ECB, Ispra, Italy 2005. http://ecbqsar.jrc.it/oasis/User_Manual_Danish_Database.pdf (Accessed 28.11.2006)
124. ESIS (European chemical Substances Information System), JRC 2006. <http://ecb.jrc.it/esis/> (Accessed 28.11.2006)
125. ToxTree v. 1.0, Ideaconult Ltd., Sofia, Bulgaria. Software and manual available: http://ecb.jrc.it/QSAR/qsar_tools/qsar_tools_toxtree.php (Accessed 28.11.2006)
126. Worth, A., Role of the ECB in promoting (Q)SARs and related estimation methods for REACH implementation, presentation held at QSAR 2006, Lyon, France, 8-12 May 2006. http://ecb.jrc.it/DOCUMENTS/QSAR/INFORMATION_SOURCES/PRESENTATIONS/Worth_Lyon_0605.pdf (Accessed 28.11.2006)
127. TerraQSAR™ FHM, Fathead minnow 96-hr LC50 Estimation Software v.1.1, TerraBase Inc., Ontario, Canada, 2006. <http://www.terrabase-inc.com/tq-4fhm.htm> (Accessed 28.11.2006)
128. Codename AMBIT, Building blocks for a future (Q)SAR decision support system, developed by Jeliazkova, N. and Jaworska, J. <http://ambit.acad.bg/> (Accessed 28.11.2006)
129. Pavan, M., Netzeva, T.I. and Worth, A., QSAR Modelling of the Bioconcentration Factor (BCF) in Fish by Molecular Attributes, poster presented at QSAR 2006, Lyon, France, 8-12 May 2006. http://ecb.jrc.it/DOCUMENTS/QSAR/INFORMATION_SOURCES/PRESENTATIONS/Pavan_Lyon_0605_poster.pdf (Accessed 28.11.2006)
130. Bassan, A., Eisenreich, S., Sokull-Kluetten, B. and Worth, A., The role of the European Chemicals Bureau in the risk assessment of nanomaterials. Is there a future for "computational nanotoxicology"?, poster presented at QSAR 2006, Lyon, France, 8-12 May 2006. http://ecb.jrc.it/DOCUMENTS/QSAR/INFORMATION_SOURCES/PRESENTATIONS/Bassan_Lyon_0605_poster.pdf (Accessed 28.11.2006)

131. Tsakovska, I., Gallegos, A., Netzeva, T., Pavan, M. and Worth, A., Evaluation of structure-activity relationships for the prediction of eye irritation and corrosion potential, poster presented at QSAR 2006, Lyon, France, 8-12 May 2006.
http://ecb.jrc.it/DOCUMENTS/QSAR/INFORMATION_SOURCES/PRESENTATIONS/Tsakovska_Lyon_0605_poster.pdf (Accessed 28.11.2006)
132. Patlewicz, G., Pavan, M., Saliner, A.G., Netzeva, T., Bassan, A., Tsakovska, I. and Worth, A., Computational toxicology at the European Chemicals Bureau (ECB), poster presented at SETAC Europe 16th Annual Meeting, Hague, 7-11 May 2006.
http://ecb.jrc.it/DOCUMENTS/QSAR/INFORMATION_SOURCES/PRESENTATIONS/Patlewicz_SETAC_0605_poster_action.pdf (Accessed 28.11.2006)
133. Anon., Report on the advisory list for self-classification of dangerous substances, Environmental project no. 636, Miljøstyrelsen (Danish Environmental Protection Agency), 2001, 39 p.
134. *Technical Guidance Document on Risk Assessment. Part 2*, 2. Ed., European Commission, Joint Research Centre, Ispra, Italy 2003, EUR 20492 EN/2, 329 p.
135. *Technical Guidance Document on Risk Assessment. Part 4*, 2. Ed. (2003), European Commission, Joint Research Centre, Ispra, Italy 2003, EUR 20492 EN/4, 276 p.
136. Idänpää-Heikkilä, J.E., Ethical principles for the guidance of physicians in medical research – the Declaration of Helsinki, *Bull. World Health Organ.* **79** (2001) p.279.
137. European Union Risk Assessment Report. 4-tert-butyl-2',6'-methyl-3',5'-dinitroacetophenone (musk ketone), Vol.62, EUR 21507 EN, Editors: S.J. Munn, R. Allanou, K. Aschberger, F. Berthault, O. Cosgrove, M. Luotamo, S. O'Connor, S. Pakalin, A. Paya-Perez, G. Pellegrini, S. Scheer, B. Schwarz-Schulz, and S. Vegro, Final report, Netherlands, 2005, 117 p.
138. European Union Risk Assessment Report. 5-tert-butyl-2,4,6-trinitro-m-xylene (musk xylene), Vol 55, EUR 21506 EN, Editors: S.J. Munn, R. Allanou, K. Aschberger, F. Berthault, O. Cosgrove, M. Luotamo, S. O'Connor, S. Pakalin, A. Paya-Perez, G. Pellegrini, S. Scheer, B. Schwarz-Schulz, and S. Vegro, Final report, Netherlands, 2005, 143 p.
139. Marquart, J., Brouwer, D.H., Gijsbers, J.H.J., Links, I.H.M., Warren, N. and Van Hemmen, J. J., Determinants of dermal exposure relevant for exposure modelling in regulatory risk assessment, *Ann. Occup. Hyg.*, **47** (2003) pp.599-607.
140. Woskie, S.R., Sparer, J., Gore, R.J., Stowe, M., Bello, D., Liu, Y., Youngs, F., Redlich, C., Eisen, E. and Cullen, M., Determinants of Isocyanate Exposures in Auto Body Repair and Refinishing Shops, *Ann. Occup. Hyg.*, **48** (2004) pp.393-403.
141. Säämänen, A., Methods to control styrene exposure in the reinforced plastics industry, VTT Publications 354, ISBN 951-38-5250-4, VTT, Espoo 1998, 83 p. + app. 63 p.
<http://www.vtt.fi/inf/pdf/publications/1998/P354.pdf> (Accessed 28.11.2006)
142. Säämänen, A., Niemelä, R., Blomqvist, T., and Nikander, E., Emission of styrene during the hand lay-up molding of reinforced polyester, *Appl. Occup. Environ. Hyg.*, **6** (1991) pp.790-793.
143. Säämänen, A. and Skrifvars, M., The effect of spraying and rolling process factors on styrene emission during the application of unsaturated polyester resins, *Am. Ind. Hyg. Assoc. J.*, **63** (2002) pp.474-481.
144. Rosen, G., Andersson, I.M., Walsh, P.T., Clark, R.D.R., Säämänen, A., Heinonen, K., Riipinen, H. and Pääkkönen, R., A review of video exposure monitoring as an occupational hygiene tool, *Ann. Occup. Hyg.*, **49** (2005) pp.201-217.
145. UK Health and Safety Executive's Control of Substances Hazardous to Health Regulations Essentials.
<http://www.coshh-essentials.org.uk/> (Accessed 28.11.2006)
146. Jackson, H., Control banding – practical tools for controlling exposure to chemicals, *Asian-Pacific Newsletter on Occupational Health and Safety*, **9** (2002) pp.62-63.
147. Kemi-Arvi 3.1., Tksoft Oy 2006.
<http://kemi-arvi.tksoft.com/> (Accessed 28.11.2006)
148. Säämänen, A., Anttila, A., and Pfäffli, P., *Occupational Exposure Agents: Styrene* (in Finnish) Helsinki, Työterveyslaitos Työsuojelurahasto TSR 1991, 29 p.
149. Pfäffli, P. and Säämänen, A., *The Occupational Scene of Styrene. Butadiene and Styrene Assessment of Health Hazards*, IARC Scientific Publications No. 127 (1993).
150. Saarela, K., Villberg, K. and Lukkarinen, T., *Emissions from Materials and Structures* (Invited paper). Healthy Buildings 2000. Espoo, FI, 6-10 August 2000, Seppänen, O. and Säteri, J. (ed). Vol.4. Finnish Society of Indoor Air Quality and Climate (FiSIAQ), pp.35-50.
151. Hakkola, M., Saarinen, L., Heinonen, K. and Säämänen, A., Customer exposure to gasoline vapours at service stations measured with the finn-pimex method, 26th International Conference on Occupational Health, International Commission on Occupational Health ICOH, Singapore, 27 August – 1 September 2000.

152. Edwards, R., Jurvelin, J., Saarela, K. and Jantunen, M., VOC concentrations measured in personal samples and residential indoor, outdoor and workplace microenvironments in EXPOLIS-Helsinki, *Atmospheric Environment*, **35** (2001) pp.4531-4543.
153. Edwards, R., Jurvelin, J., Saarela, K. and Jantunen, M., VOC source identification from personal and residential indoor, outdoor and workplace microenvironment samples in EXPOLIS-Helsinki, Finland, *Atmospheric Environment*, **35** (2001) pp.4829-4841.
154. Saarela, Kristina; Tirkkonen, Tiina; Laine-Ylijoki, Jutta; Jurvelin, J.; and Jantunen, M., Exposure of population and microenvironmental distributions of volatile organic compound concentrations in the EXPOLIS study, *Atmospheric Environment*, **37** (2003) pp.5563-5575.
155. Saarela, K. and Järnström, H., Indoor air quality in new residential buildings and behaviour of materials in structures, *Indoor and Built Environment*, **12** (2003) pp.243-247.
156. Edwards, R.D., Schweizer, C., Jantunen, M., Lai, H.K., Bayer-Oglesby, L., Katsouyanni, K., Nieuwenhuijsen, M., Saarela, K., Sram, R., and Kunzli, N., Personal exposures to VOC in the upper end of the distribution-relationships to indoor, outdoor and workplace concentrations, *Atmospheric Environment*, **39** (2005) pp.2299-2307.
157. Christensen, F.M., de Bruijn, J.H.M., Hansen, B.G., Munn, S.J., Sokull-Klüttgen, B. and Pedersen, F., Assessment tools under the new European Union chemicals policy, *GMI*, **41** (2003) pp.5-19.
158. Wahlström, M., Laine-Ylijoki, J., Hjelmar, O., Bendz, D. and Rosqvist, H. 2006. Models for impact evaluation on landfill – aspects for appropriate modelling. Nordic Innovation Centre. Technical report
159. Harmonised methods for assessment of release of dangerous substances from construction materials. Funded by Nordtest. Project team: VTT, DHI (Denmark) and SGI (Sweden).
160. Chemical and Environmental Sampling -Quality through Accreditation, Certification and Industrial Standards", Radisson SAS Hotel Brussels, Belgium, 14-15 April 2005. Arrangement of International Workshop in cooperation with Nordic Innovation Centre, CEN, Eurachem, Eurolab & VTT, Proceedings. Eds. Komppa, V., Wahlström, M. and Laine-Ylijoki, J., 134 p.
161. Wahlström, M., Eskola, P., Laine-Ylijoki, J., Leino-Forsman, H., Mäkelä, E., Olin, M. and Juvankoski, M. 1999. Risk assessment of industrial by-products used in earth construction (in Finnish). Espoo: Valtion teknillinen tutkimuskeskus. 79 p. + app. 54 p. (VTT Research Notes 1995)
162. Several risk assessments of lead contaminated sites, e.g. Malmi and Viikki shooting ranges, former lead smelter area in Vantaa, etc.
163. Several risk assessments of other metal contaminated sites.
164. Several risk assessments of risks of TBT containing sediments, for example, in Rauma and Naantali.
165. Integrated Pollution Prevention and Control Reference Document on Best Available Techniques in Common Waste Water and Waste Gas Treatment / Management Systems in the Chemical Sector, European Integrated Pollution Prevention and Control Bureau 2003.
<http://eippcb.jrc.es/pages/FActivities.htm> (Accessed 28.11.2006)
166. Anon., *Technical Guidance Document on preparing the Chemical Safety Report under REACH – Preliminary Guidance Document on preparing the Chemical Safety Assessment under REACH –Phase 1B (REACH Implementation Project 3.2-1B)*, Cefic et al. 2005, Service Contract Number 22552-2004-12 F1SC ISP BE, 767 p.
167. Chen, C.-C., Lehtimäki, M. and Willeke, K., Loading and filtration characteristics of filtering facepieces, *Am. Ind. Hyg. Assoc. J.*, **54** (1993) pp.51-60.
168. Chen, C.-C., Lehtimäki, M. and Willeke, K., Aerosol penetration through filtering facepieces and respirator cartridges, *Am. Ind. Hyg. Assoc. J.*, **53** (1992) pp.566-574.
169. Krishnan, U., Willeke, K., Juozaitis, A., Lehtimäki, M. and Szewczyk, K., Development of a dichotomous-flow quantitative fit test for half-mask and full-facepiece, *Am. Ind. Hyg. Assoc. J.*, **55** (1994) pp.223-229.
170. Willeke, K., Chen, C.-C., Myojo, T., Weber, A., Krishnan, U., Juozaitis, A., Marchioni, R. and Lehtimäki, M., Filtration, loading and face seal leakage characteristics of filtering facepieces, *J. Aerosol Science*, **23** (1992) pp.5749-5752.
171. Harms-Ringdahl, L., Jansson, T., and Malmén, Y., Safety, health and environment in small process plants – Results from a European survey, *J. Safety Res.*, **31** (2000) pp.71-80.
172. Rouhiainen, V. and Malmén, Y., Modified potential problem analysis. A versatile tool for identification of environmental risks, *Int. J. Environ. Conscious Design & Manufacturing*, **2** (1993) pp.23-26.
173. Malmén, Y., Tiihonen, J. and Wessberg, N., Management of accidental releases in the forest industry, *Water Sci. Tech.*, Vol.40 (1999) pp.313-317.
174. Kulmala, I., Numerical calculation of air flow fields generated by exhaust openings, *Ann. Occup. Hyg.*, **37** (1993) pp.451-467.
175. Kulmala, I., Numerical simulation of a local ventilation unit, *Ann. Occup. Hyg.*, **38** (1994) pp.337-349.
176. Kulmala, I., Numerical simulation of the capture efficiency of an unflanged rectangular exhaust opening in a coaxial air flow, *Ann. Occup. Hyg.*, **39** (1995) pp.21-33.

177. Kulmala, I., Numerical simulation of unflanged rectangular exhaust openings, *Am. Ind. Hyg. Assoc. J.*, **56** (1995) pp.1099-1106.
178. Kulmala, I., *Advanced design of local ventilation systems*, VTT Publications No 307, VTT Espoo 1997, ISBN 951-38-5052-8, 80 p. + app. 111 p.
179. Kulmala, I., Air flow near a welding exhaust hood, *Appl. Occup. Environ. Hyg.*, **12** (1997) pp.101-104.
180. Kulmala, I., Säämänen, A. and Enbom, S., The effect of contaminant source location on worker exposure in the near-wake region, *Ann. Occup. Hyg.*, **40** (1996) pp.511-523.
181. Kulmala, I. and Saarenrinne, P., Numerical calculation of an air flow field near an unflanged circular exhaust opening, *Staub-Reinhaltung der Luft*, **55** (1995) pp.131-135.
182. Säämänen, A., Andersson, I.-M., Niemelä, R. and Rosen, G., Assessment of horizontal displacement flow with tracer gas pulse technique in reinforced plastic plants, *Building and Environment*, **30** (1995) pp.135-141.
183. Welling, I., Kulmala, I., Andersson, I.-M., Rosen, G., Mielo, T., Marttinen, K., Säämänen, A. and Niemelä, R., Extent of the reverse flow wake region produced by a body in a uniform flow field, *Appl. Occup. Environ. Hyg.*, **164** (2001) pp.900-904.
184. Heinonen, K., Kulmala, I. and Säämänen, A., Local ventilation for powder handling – combination of local supply and exhaust air, *Am. Ind. Hyg. Assoc. J.*, **57** (1996) pp.356-364.
185. Kulmala, I., Hynynen, P., Welling, I. and Säämänen, A., Local ventilation solution for large, warm emission sources, *Ann. Occup. Hyg.* (accepted, Annals of Occupational Hygiene Advance Access published July 20, 2006).
186. Lehtimäki, M. and Heinonen, K., Reliability of electric filters, *Building and Environment*, **29** (1994) pp.353-355.
187. Lehtimäki, M. and Taipale, A., The facts about mechanical grease filters, *Aschrae J.*, June 2003, pp.14-17.
188. *Reach Implementation Project 3.9-1: Preliminary Study for A Technical Guidance Document on Carrying Out A SEA or Input for One*, Final Report – Part A and B, RPA and SYKE 2006, Service contract number: CCR.IHCP.C430310.X0, 162 p.
189. Anastas, P.T. and Williamson, T.C., Green chemistry: An overview, in *Green Chemistry, Designing Chemistry for the Environment*, Eds. Anastas, P.T. and Williamson, T.C., ACS Symp. Ser. **626**, American Chemical Society, Washington 1996.
190. Anastas, P.T. and Warner, J.C., *Green Chemistry: Theory and Practice*, Oxford Science publication, Oxford (1998).
191. Poliakoff, M., Fitzpatrick, J.M., Farren, T.R. and Anastas, P.T., Green chemistry: Science and politics of change, *Science* **297** (2002) pp.807-810.
192. Poliakoff, M. and King, P.J., Phenomenal fluids, *Nature* **412** (2001) p.125.
193. Anastas, P.T. and Kirchoff, M.M., Origins, current status, and future challenges of green chemistry, *Acc. Chem. Res.*, **35** (2002) pp.686-694.
194. Kazarian, S.G., Briscoe, B.J. and Welton, T., Combining ionic liquids and supercritical fluids: *in situ* ATR-IR study of CO₂ dissolved in two ionic liquids at high pressures, *Chem. Commun.* (2000) pp.2047-2048.
195. Cave, G.W.V., Raston, C.L. and Scott, J.L., Recent advances in solventless organic reactions: towards benign synthesis with remarkable versatility, *Chem. Commun.* (2001) pp.2159-2169.
196. Tundo, P., Anastas, P., StC. Black, D., Breen, J., Collins, T., Memoli, S., Miyamoto, J., Polyakoff, M. and Tumas, W., Synthetic pathways and processes on green chemistry. Introductory overview, *Pure Appl. Chem.*, **72** (2000) pp.1207-1228.
197. Anon., *Safer Chemicals within REACH. Using the Substitution Principle to drive Green Chemistry*, Greenpeace European Unit, Brussels 2005, ISBN: 1-903907-07-1, 38 p.
198. Anon., *Voluntary Approaches for Environmental Policy. Effectiveness, Efficiency and Usage in Policy Mixes*, OECD, Paris, France, 2005, ISBN: 92-64-10177-2, 144 p.
199. Reinert, K.H., Integrating green chemistry and sustainability into a specialty chemical company, *Pure Appl. Chem.*, **73** (2001) pp.1269-1272.
200. Lohse, J., Wirts, M., Ahrens, A., Heitmann, K., Lundie, S., Lißner, L. and Wagner, A., *Substitution of Hazardous Chemicals in Products and Processes*, Report compiled for the Directorate General Environment, Contract No B3-4305/2000/293861/MAR/E1, Hamburg, Germany, 2003, 109 p.
201. Kaunisto, T. and Carpen, L., *Kaukolämpöverkoissa käytettävien vedenkäsittelykemikaalien toimivuuden tutkiminen*, VTT Raportti VALB324, 1998.
202. Anon., *OECD Guiding Principles for Chemical Accident Prevention, Preparedness and Response*, **2. Ed.**, OECD Environment, Health and Safety Publications, Paris, France, 2003, 210 p.
203. Oggero, A., Darbra, R.M., Muñoz, M., Planas, E. and Casal, J., A survey of accidents occurring during the transport of hazardous substances by road and rail, *J. Haz. Mat.*, **A133** (2006) pp.1-7.
204. Whiteley, J.R.R. and Mannan, M.S., Initial perspectives on process threat management, *J. Haz. Mat.*, **115** (2004) pp.163-167.
205. Fragola, J., The human element in operating safety, Discussion document in *Report of the OECD Workshop on Human Performance in Chemical Process Safety: Operating Safety in the Context of Chemical Accident*

- Prevention, Preparedness and Response.*, ENV/JM/MONO(99)12, OECD Environmental Directorate, Paris 1999, pp.23-34.
206. Kletz, T.A., What you don't have, can't leak, *Chem. Ind.*, **6** (1978) pp.287-292.
 207. Hendershot, D.C., Inherently safer chemical process design, *J. Loss. Prev. Process Ind.*, **10** (1997) pp.151-157.
 208. Khan, F.I. and Amyotte, P.R., How to make inherent safety practice a reality, *Can. J. Chem. Eng.*, **81** (2003) pp.2-16.
 209. Study, K., A real-life example of choosing an inherently safer process option, *J. Haz. Mat.* (2006), doi:10.1016/j.hazmat.2006.06.097.
 210. Gupta, J.P. and Edwards, D.W., Inherently safer design-present and the future, *Trans. IChemE B Process Saf. Environ. Protect.*, **80** (2002) pp.115-125.
 211. Heikkilä, A.-M., *Inherent Safety in Process Plant Design. An Index-Based Approach*, Doctoral thesis, VTT Technical Research Centre of Finland, Espoo, 1999, 129 p.
 212. Gentile, M., Rogers, W.J. and Mannan, M.S., Development of an inherent safety index based on fuzzy logic, *AIChE J.*, **49** (2003) pp.959-968.
 213. Hurme, M. and Heikkilä, A.-M., Applications of genetic optimisation and case-based reasoning for synthesis of inherently safer chemical processes, 3rd IFIP Working Group 5.2 Workshop on Knowledge Intensive CAD (KIC-3). Tokyo, Japan, 1-4 December. 1998. pp.210-221.
 214. Heikkilä, A.-M. and Hurme, M., Inherent safety index for offsite equipment in preliminary process design, 13th International Congress of Chemical and Process Engineering CHISA'98. 23-28 November 1998. Czech Society of Chemical Engineering. Prague, Czech Republic, 10 p.
 215. Heikkilä, A.-M., Koironen, T. and Hurme, M., Safety evaluation of process configuration by case-based reasoning, 13th International Congress of Chemical and Process Engineering CHISA'98. 23-28 November 1998. Czech Society of Chemical Engineering. Prague, Czech Republic, 14 p.
 216. Hurme, M. and Heikkilä, A.-M., Conceptual design of inherently safer processes by genetic algorithms and case-based reasoning, Proceedings of Pres'99 2nd Conference on Process Integration, Modelling, and Optimisation for Energy Saving and Pollution Reduction. Budapest, Hungary, 31 May - 2 June 1999. Friedler, F. and Klemens, J., Hungarian Chemical Society. Budapest, Hungary, pp.341-346.
 217. Srinivasan, R., Chia, K.C., Heikkilä, A.-M. and Schabel, J., Supporting design through a database of inherently safer processes, *Loss Prev. Bull.* (2004) No: 177, pp.16-25.
 218. Rahman, M., Heikkilä, A.-M. and Hurme, M., Comparison of inherent safety indices in process concept evaluation, *J. Loss Prev. Process Ind.*, **18** (2005) pp.327-334.
 219. Khan, F.I. and Amyotte, P.R., Integrated inherent safety index (I2SI): A tool for inherent safety evaluation, *Process Saf. Process*, **23** (2004) pp.136-148.
 220. Cozzani, V., Smeder, M. and Zanelli, S., Formation of hazardous compounds by unwanted reactions in industrial accidents, *J. Haz. Mat.*, **A63** (1998) pp.131-142.
 221. Nomen, R., Sempere, J., Pey, A. and Alvarez, A., Solving the Seveso II problem of substance generation during loss of control by AI techniques, *J. Loss Prev. Process Ind.*, **16** (2003) pp.55-60.
 222. Lunghi, A., Gigante, L., Cardillo, P., Stefanoni, V., Pulga, G. and Rota, R., Hazard assessment of substances produced from the accidental heating of chemical compounds, *J. Haz. Mat.*, **A116** (2004) pp.11-21.
 223. Saraf, S.R., Rogers, W.J. and Mannan, M.S., Using screening test data to recognise reactive chemical hazards, *J. Haz. Mat.*, **104** (2003) pp.255-267.
 224. Marsanich, K., Barontini, F., Cozzani, V., Creemers, A. and Kersten, R., Different scale experimental techniques to approach the problem of substances generated in the loss of control of chemical systems: A study on ethyl diazoacetate decomposition, *J. Loss Prev. Process Ind.*, **17** (2004) pp.9-22.
 225. Laitinen, A., Räsänen, L. and Koukkari, P., Kalorimetria auttaa parantamaan kemikaali- ja prosessiturvallisuutta, *Kemia*, **31** (2004) pp.37-39.
 226. Lempert, R.J., Norling, P., Pernin, C., Resetar, S. and Mahnovski, S., *Next Generation Environmental Techniques. Benefits and Barriers*, RAND Science and Technology Policy Institute, Santa Monica CA 2003, ISBN:0-8330-3417-0, 198 p.
 227. Anon., *Technology Vision 2020. The U.S. Chemical Industry*, American Chemical Society, The American Institute of Chemical Engineers, The Chemical Manufacturers Association, The Council for Chemical Research and The Synthetic Organic Chemical Manufacturers Association 1996, 75 p.
 228. Anon., *New Process Chemistry. Technology Roadmap*, American Chemical Society, 2001, 24 p.
 229. Laitinen, A., *Supercritical Fluid Extraction of Organic Compounds from Solids and Aqueous Solutions*, Dissertation thesis, VVT Espoo 1999, ISBN 951-38-5551-1, 58 p.
 230. Laitinen, A. and Jäntti, M., Solubility of 6-Caprolactam in Supercritical Carbon Dioxide, *J. Chem. Eng. Data*, **41** (1996) pp.1418-1420.
 231. Laitinen, A. and Kaunisto, J., Hydrodynamics and Mass Transfer in a Rotating Disc Supercritical Extraction Column, *Ind. Eng. Chem. Res.*, **37** (1998) pp.2529-2534.

232. Laitinen, A. and Kaunisto, J., Oldshue-Rushton Column in Supercritical Fluid Extraction, *Sep. Sci. Tech.*, **34** (1999) pp.1859-1872.
233. Laitinen, A. and Kaunisto, J., Supercritical Fluid Extraction of 1-Butanol from Aqueous Solutions, *J. Supercritical Fluids*, **15** (1999) pp.245-252.
234. Ojaniemi, U., Olin, M., Pättikangas, T., Seppälä, M., Taivassalo, V., Aittamaa, J., Alopaeus, V., Hynynen, K., Jussila, S., Laakkonen, M., Liiri, M., Moilanen, P., Nurmela, A., Pulkkinen, I., Alatalo, H., Hatakka, H., Kallas, J., Laari, A., Zuoliang, S., Turunen, I., Hermanson, A., Kallio, S., Eloranta, H., Honkanen, M., Saarenrinne, P. and Saikkonen, T., *Modelling of Multiphase Chemical Reactors (ModCheR)*, Final report, Ed. M. Manninen, VTT Research Notes 2340, VTT Espoo 2006, ISBN 951-38-6793-5, 181 p.
235. Ojaniemi, U. and Manninen, M., *Three Phase CFD Modelling of Flotation*, Report VTT-R-02999-06, VTT Espoo 2006.
236. Manninen, M. and Ojaniemi, U., *Population Models for Bubbly Flow in A Stirred Reactor*, Report VTT-R-02997-06. VTT Espoo 2006.
237. Olin, M., Manninen, M. and Pättikangas, T., *k-ε Turbulence Model for Polymeric Drag Reduction*, Project report PRO5/P5020/05, VTT Espoo 2005.
238. Ojaniemi, U., Manninen, M. and Taivassalo, V., *CFD Modelling of Turbulent Fluidised Bed*, Report PRO5/P5025/05, VTT Espoo 2005.
239. Seppälä, M., *Kaasu-partikkelivirtausten numeeriset laskentamenetelmät*, Master's thesis, VTT Espoo 2006.
240. Sirén, H., Luomanperä, K., Työppönen, T., Rovio, S., Vastamäki, P. and Savolahti, P., Process control and drug analysis with an on-line capillary electrophoresis system, *J. Biochem. Biophys. Methods*, **60** (2004) pp.295-307.
241. Chemsheet – A New Spreadsheet Tool for Process Simulation. GTT Technologies, Herzogenrath, Germany. <http://www.chemsheet.com/> (Accessed 28.11.2006)
242. Koukkari, P., Pakarinen, H. and Leino, H., Hiilidioksidi hyötykäyttöön paperitehtaassa, *Kemia*, **29** (2002) pp.24-27.
243. Martin, A.R., Drotz, M., Talja, R., Kaijaluoto, S. and Puumalainen, T., Energy analysis of impulse technology: Research scale experimental papermaking trials and simulations of industrial applications, *Appl. Thermal Eng.*, **24** (2004) pp.2411-2425.