



# **REACH – SUMMARY OF THE LEGISLATION AND REQUIREMENTS FOR INDUSTRY**

**Author: H. Barnes and L. McLaughlin**

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**Peter Fisk Associates Ltd**

Registered address: 14 Darenth Close, Herne Bay, Kent CT6 7EX, UK

Tel: (+44)(0)208 123 6265 ♦ Mobile: (+44)(0)7795 517615

Web Site: <http://www.ecotoxchem.co.uk>

*Company Number 5758319 (England and Wales) ♦ VAT Number: GB 661706927*

# REACH – SUMMARY OF THE PROPOSALS AND LIKELY REQUIREMENTS FOR INDUSTRY

## 1. Current Status

REACH, the new EU chemicals legislation, entered into force on 1<sup>st</sup> June 2007. Its full title is Regulation (EC) no 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

Previously there were 40 community Directives and Regulations on chemicals, with separate rules for new and existing chemicals. The REACH proposal is a complete review of the regulation of chemicals in the EU replacing the existing legislation with a single Regulation which has a consistent approach for new and existing chemicals.

The following legislation is repealed by the REACH Regulation:

- Council Regulation (EEC) No 793/93 (Existing Substances Regulation)
- Commission Regulation (EC) No 1488/94 (Risk assessment of existing substances)
- Council Directive 76/769/EEC (Marketing and Use)
- Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

REACH also amends Directive 1999/45/EC (Dangerous Preparations Directive), and the Directive 67/548/EEC (Dangerous Substances Directive) has been adapted to the REACH Regulation by Directive 2006/121/EC, such that existing symbols, risk and safety phrases will apply for an interim period under REACH until the Globally Harmonised System is formally adopted in the EU.

A new agency, the European Chemicals Agency ([ECHA](#)) has been set up to manage the technical, scientific and administrative aspects of REACH.

The Agency will manage the registration process and will undertake dossier evaluation (compliance check and evaluation of testing proposals). It will also be coordinating action in substance evaluation, and establish and run the IT infrastructure. It has significant decision-making powers, and judicial review is provided by a Board of Appeal.

Through its expert Committees, the ECHA will advise the Commission on the authorisation procedure and applications for authorisations, and on risk reduction measures for dangerous substances (restrictions).

Registration of new chemicals began on 1<sup>st</sup> June 2008. Pre-registration of “phase-in” (“existing”) chemicals also began on 1<sup>st</sup> June 2008, and must be completed by 1<sup>st</sup> December 2008. Any company manufacturing or importing chemicals in the EU had to pre-register in order to take advantage of the later deadlines that exist for “phase-in” chemicals. Over 2 million pre-registrations were submitted in this phase, which is now closed.

Further information on pre-registration:

- [Q&A on pre-registration](#)

The first phase of registrations is due for completion before 1st December 2010. There are a number of industry initiatives to help:

The Chemicals Industry Association has launched [REACHReady](#), a Service network which provides information and tools, and links clients with service providers (e.g. contract laboratories, consultants) through its Matchmaker facility.

Cefic has set up [ReachCentrum](#) to facilitate the preparation for and implementation of REACH, initially with help desk services. [Peter Fisk Associates](#) is able to provide expert services to help with REACH compliance and is a REACHReady-approved service provider.

## 2. Why REACH?

The aim of REACH is to protect human health and the environment whilst enhancing innovative capability and maintaining competitiveness of EU chemical industry.

Legislation regulating chemicals has historically had several drawbacks that have led to it being ineffective and slow in identifying risks, and a disincentive to innovation:

- Encouraged use of existing chemicals
- Distinguished between "existing" (pre-1981) and "new" (post-1981) chemicals, requiring notification and testing for new chemicals (in production volumes of 10 kg and above), but not for old. This inhibited research and development of new chemicals: since 1981 only around 3,000 new chemicals have been put on the market.
- Implemented in a manner which does not allow for a large number of substances to be reviewed.
- Responsibility for determining selecting existing chemicals for examination, and carrying out risk assessment has rested with the Competent Authorities in each EU Member State (Health and Safety Executive and Defra in the UK). Since 1993, of the 100,106 "existing chemicals", 140 high volume chemicals have been selected for risk assessment, and only a fraction has completed the process.

A more detailed comparison of previous legislation and REACH is given in the table below.

Previous system	REACH
The authorities must prove that the use of a chemical substance is unsafe before they may impose restrictions.	Industry will have to take responsibility for assessing the risks of chemicals and for ensuring their safe use.
There are gaps in our knowledge about many of the chemicals on the European market.	REACH will provide safety information about chemicals produced or imported in volumes higher than 1 tonne/year per manufacturer/importer.
Notification requirements for 'new substances' start at a production level of 10 kg. At this level, one animal test is needed. At 1 tonne, additional animal tests are required.	Registration will be required when production/import reaches 1 tonne. As far as possible, animal testing will be minimised, and focussed on where real need exists for the data.
The cost of introducing a new substance on the market encourages the continued use of "existing", untested chemicals and inhibits innovation.	Registration costs for new substances will be lower under REACH, and innovation less discouraged.
Public authorities are obliged to perform comprehensive risk assessments that are slow and cumbersome.	Industry will be responsible for assessing the safety of identified uses, prior to production and marketing. Authorities will be able to focus on issues of serious concern.

### 3. Timescale of REACH

The REACH Regulation was first proposed in 2003, and finally adopted by the Council of Ministers in December 2006.

The Regulation came into force on 1<sup>st</sup> June 2007. As a Regulation (rather than a Directive), REACH does not need to be transposed into national legislation, as Regulations become part of Member State Legislation once they are passed.

#### Read the text of the [REACH Regulation](#)

Substances that have not been manufactured or imported into the EU previously have needed to be registered under REACH before manufacture or importation (at 1 tonne per year or more), since 1st June 2008. Three weeks will elapse between submitting the dossier and commencing manufacture or import to allow the dossier to be checked.

Existing substances (those listed on [EINECS](#)<sup>1</sup>) will be phased-in to REACH. The following deadlines apply:

- 1 June 2008 onwards registration of new chemicals produced in quantities of 1 tonne or more is mandatory. PPORD notifications may be required for chemicals under development.
- The Agency will make publicly available the list of all pre-registered substances by 1 January 2009.

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<sup>1</sup> EINECS European INventory of Existing Commercial chemical Substances

- 30 November 2010: substances produced or imported in high volumes (1,000 tonnes or more per year per manufacturer or importer), CMRs<sup>2</sup> (>1 tonne/year) and substances classified as very toxic to aquatic organisms (R50/53) (> 100 tonnes/year) will have to be registered.
- 31 May 2013: Registration of substances with production or import volumes in the 100-1,000 tonne range
- 31 May 2018: Registration of all remaining substances.

Substances that have previously been notified as new substances (listed on ELINCS<sup>3</sup>) will be treated as having been registered under REACH.

Substances contained in articles (and hence exempt from registration), which are on the “candidate list of substances of very high concern” will need to be reported to the European Chemicals Agency from 1 June 2011.

Substances of very high concern are

- carcinogens, mutagens, substances toxic to the reproductive system, (CMR)
- substances which are persistent, bio-accumulative and toxic, (PBT)
- very persistent and very bio-accumulative (vPvB)
- or of equivalent concern (e.g. endocrine disrupting substances which disturb the body’s hormone system)

## 4. REACH general procedure

**Registration** For all substances manufactured or imported in volumes greater than 1 tonne per annum, the manufacturer or importer must gather information on:

- Properties
- Identified uses
- Safe management.

Manufacturers and importers will submit registration dossiers - information in a standardised format - demonstrating that chemicals are being managed safely.

**Dossiers** Details of the contents of registration dossiers can be found in Annex XV of the Regulations. For substances in the 1-10 tonnes per annum range, dossiers will include safety information produced for the safety data sheets. For volumes of 10 tonnes and above, a Chemical Safety Report assessing risks for human health and the environment, and how those risks are controlled for the

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<sup>2</sup> CMRs are substances which are carcinogenic, mutagenic or toxic to reproduction

<sup>3</sup> ELINCS: European List of Notified Chemical Substances

identified uses, will be required as part of registration. Proposals for “higher tonnage level” testing are also submitted.

**Evaluation** Dossier evaluation will be conducted by the European Chemicals Agency (see Section 1), to decide on proposals for further testing and assess whether the information supplied in the dossier complies with registration requirements, and to ensure that unnecessary animal testing is avoided.

Substance evaluations can be performed when there is reason to believe that a substance may present a risk to human health or the environment, and will look at all the registration dossiers submitted for the same substance. The Competent Authorities in the Member States will be responsible for performing evaluations.

There are three possible outcomes of the evaluation:

- no further action
- more information requested
- further regulation required

If substances pose unacceptable risks, restrictions on use or a complete ban may be imposed. Substances with very hazardous properties will be subject to authorisation.

**Authorisation** For substances of very high concern<sup>4</sup>, use-specific permission from the Commission will be required. The manufacturer or importer must show that risks can be controlled. Substances of very high concern are PBTs (persistent, bio-accumulative and toxic) vPvBs (very persistent, very bio-accumulative) and CMRs (carcinogenic, mutagenic or toxic to reproduction) and endocrine disrupting chemicals.

The Commission would also be able to introduce restrictions at EU level on substances that needed to be managed on an EU-wide scale to ensure that the risks they posed were acceptable.

The Safety Data Sheets (SDS) used for hazard communication in the previous system will continue to be used in REACH, although some changes to the format are required, and information on exposure scenarios relevant to users are to be included. The [Safety Data Sheet requirements](#) under REACH are covered in part G of the REACH [Guidance on information requirements and chemical safety assessment](#).

There are a number of exemptions from registration:

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<sup>4</sup> Substances of very high concern are: carcinogens, mutagens, substances toxic to the reproductive system, (CMR); substances which are persistent, bio-accumulative and toxic, (PBT); very persistent and very bio-accumulative (vPvB); or of equivalent concern (e.g. endocrine disrupting substances which disturb the body's hormone system)

- Radioactive substances, non-isolated intermediates, waste and substances which are subject to customs supervision under certain conditions (Art. 2 (1) (b)) are outside the scope of the REACH Regulation and therefore do not have to be registered
- Substances exempted from present legislation are also exempt from REACH. These are listed in Annex IV
- Substances fulfilling criteria listed in Annex V are exempt from REACH. This includes some substances occurring in nature (e.g. minerals, crude oil), if they are not chemically modified), and elemental substances for which hazards and risks are well known (hydrogen, oxygen, nitrogen and noble gases).

Also exempt from registration are substances used:

- In medicinal products for human or veterinary use
- As a food additive in foodstuffs
- As a flavouring in foodstuffs
- As an additive in feedingstuffs
- In animal nutrition.

Polymers are exempted from registration and evaluation but they may still be subject to authorisation and restriction, and the monomers from which it is manufactured may need to be registered. This is covered in the [REACH Q and A](#) document and in the [guidance on polymers and monomers](#).

## 5. Data sharing

The principle of data sharing is embodied in REACH (Article 11, Joint submission of data by multiple registrants, in the text of the [Regulation](#)). There will be only one submission of hazard information for a substance, and for the Chemical Safety Report, unless a company opts out. This will be achieved by the formation of Substance Information Exchange Fora (SIEFs). In a SIEF, companies are obliged to share animal testing studies to keep the number of animals used for testing to an absolute minimum. They may also share other data voluntarily.

This is likely to mean in practice (in most cases) that groups of companies will find it time- and cost-effective to group together as consortia and share the responsibility of data gathering and collation.

Guidance on data sharing is available from [ECHA](#).

## 6. Data requirements

What follows is a summary of the test requirements. For full details, see Annex. For rules of adaptation refer also to the text of the [Regulation](#).

The test requirements are specified in Annexes VII-X to Article 13 of the REACH Regulation. Standard testing methods are detailed in Annex XI to the Regulation. The table below shows the total number of tests required which might be required at different tonnage levels:

	Physico-chemical properties	Toxicological information	Ecotoxicological information
1 - 10 tpa	14	5	1
10 - 100 tpa	14	15	7
100 - 1000 tpa	16	14-17	18
1000 tpa	16	22	16-18

At tonnages above 100 tpa (Annex IX), the need for some tests depends on the outcome of other studies, and testing strategies are available in guidance for [ecotoxicological](#) and [toxicological](#) properties. The requirement for particular tests may be waived if testing is not technically feasible, or it can be demonstrated that exposure will be low.

A more detailed summary of data requirements can be found in Appendix 1 of this review.

### 6.1 Adapting the test regime

Annex XI of the legislation, sets out for the adaptation of testing requirements. There are various scenarios where the standard testing strategy may not apply:

- Testing does not appear to be scientifically necessary. This may be because a) non-GLP data or historical human data are available; b) weight of evidence or (Q)SAR<sup>5</sup> indicate the presence or absence of a particular dangerous property; c) *in vitro* data indicates the presence of a certain dangerous property; d) grouping of substances and read across are possible.
- Testing is technically not possible: e.g. very volatile, highly reactive or unstable substances cannot be used in some studies, mixing of the substance with water may cause danger of fire or explosion or the radio-labelling of the substance required in certain studies may not be possible. This is subject to the guidelines given in Annex XI of the Regulation.

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<sup>5</sup> (Q)SAR stands for (Quantitative) structure activity relationship. It is a relationship between chemical structure and biological activity, which may be mathematical

- Substance-tailored exposure-driven testing. Exposure scenario(s) developed in the Chemical Safety Report may allow animal testing for substances in the >100 tonnage band to be omitted.

Before new tests are carried out, all available data shall be assessed, including: *in vitro* data, *in vivo* data, historical data, data from valid QSARs, and data from structurally related substances (read across approach).

## 7. Availability of guidance

The Guidance Documents available include:

- Guidance on information requirements and [chemical safety assessment](#);
- [Guidance on Registration](#);
- [Guidance for intermediates](#);
- [Guidance for monomers and polymers](#);
- [Guidance for articles](#);
- Guidance on [Scientific Research and Development \(SR&D\) and Product and Process Oriented Research and Development \(PPORD\)](#);
- Guidance on [data sharing](#)
- [Guidance for downstream users](#)
- [Chemical safety assessment for preparations](#);
- [Safety Data Sheets](#);
- [IT tools](#);
- [Guidance for identification and naming of substances in REACH](#)
- [Guidance on IUCLID](#).

[REACH IT](#) is at the heart of the European Chemical Agency. REACH IT is a paperless system for the registration of substances. [IUCLID V](#) has been developed by the OECD and must be used for the preparation of study summaries for REACH dossiers.

## **8. Chemical Safety Report**

Chemical Safety Assessment and the Preparation of Chemical Safety Reports are covered in Annex I to the [REACH Regulation](#), which includes the format for Chemical Safety Reports. Detailed guidance on the preparation of Chemical Safety Reports is available from ECHA

## **9. Authorisation issues**

### **9.1 Substances of very high concern**

Use of substances of very high concern will be subject to authorisation. Article XIII describes the criteria for the identification of PBT and vPvB substances. These criteria are very similar to the definitions that the European Chemicals Bureau's Joint Research Centre have already worked on - the commission is not waiting for industry to submit registration dossiers before evaluating chemicals already identified as of concern. Substances subject to authorisation will be listed in Annex XIV of the Regulation. The candidate list for substances of very high concern has been [published](#). Suppliers of the substances on this list must provide recipients with a Safety Data Sheet.

Use and marketing of substances included in Annex XIV will be restricted to those companies who have been granted an authorisation, and their customers. Authorisations will apply to particular uses, and may set conditions for use of the substance.

Substances of very high concern subject to authorisation but which are yet not on Annex XIV may continue to be used as long as they fulfil the other requirements placed on them under REACH and other applicable legislation.

### **9.2 Authorisation of substances in preparations**

The authorisation process will only apply to the use of substances in preparations where the substance is present in sufficient concentration for the preparation itself to be classified. For PBT or vPvB and CMR substances there is a concentration limit of 0.1% above which authorisation is required<sup>6</sup>.

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<sup>6</sup> REACH Title VII Article 56 section 6a

## **10. Substances in articles**

Substances that are intended to be released during normal use of an article (e.g. the ink in a printer cartridge) will need to be registered if the substance is present in total over 1 tonne per producer/importer/year, and if it is intended to be released. The same tonnage thresholds and information requirements as for other substances apply. Substances of very high concern in articles shall be notified when the substance is present in total over 1 tonne per producer/importer/year, and it is present at a concentration above 0.1%.<sup>7</sup> If the release is not intended as part of the functioning of the article, but happens anyway (e.g. formaldehyde released from fibreboard), the substance may have to be notified to the ECHA, who will decide whether a registration is needed. Some concern has been expressed that substances present in imported articles are not adequately covered by the REACH legislation, though presence of restricted substances in imported articles could pose a very real threat to the environment or to human health.

## **11. Substitution**

REACH is intended to be an incentive for substitution in the following ways:

- Industry is responsible for the safe management of chemicals. This includes increasing availability of hazard information and safety assessment for downstream users and the general public, which should be and incentive to replace substances of concern with less risky alternatives
- Application for authorisation is costly, and it is hoped that this will encourage investment in research to find safer alternatives
- Authorisations require lists of alternatives, so substitution will be thought about in the application process
- Demands for testing on registration increase costs which can be avoided if potentially problematic substances are replaced with well-tested, safer alternatives
- Access to information will stimulate downstream users, retailers and consumers to demand safer alternatives.

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<sup>7</sup> REACH Title 2 Article 7 section 2a

## 12. Property prediction and Regulations

There are a number of purposes for which (quantitative) structure-activity relationships ((Q)SAR) or other predictive methods could be used in principle in the implementation of legislation on chemical substances and products. They include:

- To provide information for use in priority setting procedures, which are used to expedite the risk assessment process for chemicals of concern
- To support choices made in testing strategies
- To classify chemicals on the basis of their hazardous properties
- To provide dose-response information
- To provide environmental fate information.

Currently, SARs and QSARs are used extensively for regulatory purposes in the United States and Canada. In the EU, limited use has been made of QSARs so far: they have been applied for priority setting of existing chemicals, for classification and labelling and for the prediction of environmental effects of HPVCs (High Production Volume Chemicals).

### 12.1 Grouping substances for read-across

The regulation supports a grouping or ‘category’ approach and the use of read-across where appropriate to fill data gaps. Similar uses of these approaches, and prediction methods are described in [guidance on non-testing approaches](#).

In principle the grouping of substances gives an opportunity to develop or adjust QSARs to be appropriate to that category. The use of QSAR in general is discussed in Appendix 1 of this review.

## Annex 1: Summary of data requirements

### 1-10 TPA Annex VII of Regulation

Physchem	Toxicology	Ecotoxicology
Physical state of substance at 20°C and 1014 hPa	Skin irritation/corrosivity	acute or chronic <i>Daphnia</i> (preferred species)
Melting/freezing point	Eye irritation	Algal growth inhibition
Relative density	Skin sensitisation	Biotic degradation
Vapour pressure	<i>In vitro</i> mutagenicity (bacterial)	Ready biodegradability
Surface tension	Acute oral toxicity	
Water solubility		
Partition coefficient n-octanol/water		
flash point		
flammability		
explosive properties		
self-ignition temperature		
oxidising properties		
granulometry		

## Annex 2: Summary of data requirements, 10-100 tonnes

### 10-100 TPA Annex VII and VIII of Regulation

Physchem	Toxicology	Ecotoxicology
Physical state of substance at 20°C and 1014 hPa	Skin irritation/corrosivity	acute or chronic <i>Daphnia</i> (preferred species)
Melting/freezing point	Eye irritation	Algal growth inhibition
Relative density	Skin sensitisation	Biotic degradation
Vapour pressure	<i>In vitro</i> mutagenicity (bacterial)	Ready biodegradability
Surface tension	Acute oral toxicity	Fish acute toxicity
Water solubility	<i>In vivo</i> tests skin irritation	Activated sludge respiration inhibition test
Partition coefficient n-octanol/water	<i>In vivo</i> eye irritation	Further degradation studies, depending

		on chemical safety assessment
Flash point	<i>In vitro</i> cytogenicity (mammalian)	Abiotic degradation-hydrolysis as a function of pH
Flammability	<i>In vitro</i> mutagenicity (mammalian)	Adsorption/desorption
Explosive properties	Acute oral toxicity	
Self-ignition temperature	Inhalation and/or dermal toxicity, as appropriate	
Oxidising properties	Repeated dose toxicity - 28 d	
Granulometry	Repeated dose toxicity - 90 d, if necessary	
	Reproductive toxicity	
	Toxicokinetic behaviour	

### 100-1000 TPA Annexes VII, VIII and IX

Physchem	Toxicology	Ecotoxicology
Physical state of substance at 20°C and 1014 hPa	Skin irritation/corrosivity	acute or chronic <i>Daphnia</i> (preferred species)
Melting/freezing point	Eye irritation	Algal growth inhibition
Relative density	Skin sensitisation	Biotic degradation
Vapour pressure	<i>In vitro</i> mutagenicity (bacterial)	Ready biodegradability
Surface tension	Acute oral toxicity	Fish acute toxicity
Water solubility	<i>In vivo</i> tests skin irritation	Activated sludge respiration inhibition test
Partition coefficient n-octanol/water	<i>In vivo</i> eye irritation	Further degradation studies, depending on chemical safety assessment
flash point	<i>In vitro</i> cytogenicity (mammalian)	Abiotic degradation-hydrolysis as a function of pH
flammability	<i>In vitro</i> mutagenicity (mammalian)	Adsorption/desorption
explosive properties	Acute oral toxicity	Long-term toxicity to <i>Daphnia</i>
self-ignition temperature	Inhalation and/or dermal toxicity, as appropriate	Long-term toxicity to fish, ie one of the following
oxidising properties	Repeated dose toxicity - 28 d	<i>Either:</i> Fish early life stage toxicity
granulometry	Repeated dose toxicity - 90 d, if necessary	<i>or</i> Fish embryo and sac-fry acute toxicity
Stability/degradation products in organic solvents	Reproductive toxicity	<i>or</i> Juvenile fish growth

Dissociation constant	Toxicokinetic behaviour	Degradation testing (surface water, soil, sediment) if required
Viscosity	In vivo genotoxicity tests (if Annex V or VI studies give positive results)	Identification of degradation products
	Repeated dose toxicity 28 d, if not already provided	Bioaccumulation in fish (if required)
	Sub-chronic (90-day) toxicity (if necessary)	Further adsorption/desorption studies (if required)
	Pre-natal developmental toxicity (one species)	Effects on terrestrial organisms (if appropriate)
	Two-generation reproductive toxicity	

### 1000+ TPA Annexes VII VIII XI and X

Physchem	Toxicology	Ecotoxicology
Physical state of substance at 20°C and 1014 hPa	Skin irritation/corrosivity	acute or chronic <i>Daphnia</i> (preferred species)
Melting/freezing point	Eye irritation	Algal growth inhibition
Relative density	Skin sensitisation	Biotic degradation
Vapour pressure	<i>In vitro</i> mutagenicity (bacterial)	Ready biodegradability
Surface tension	Acute oral toxicity	Fish acute toxicity
Water solubility	<i>In vivo</i> tests skin irritation	Activated sludge respiration inhibition test
Partition coefficient n-octanol/water	<i>In vivo</i> eye irritation	Further degradation studies, depending on chemical safety assessment
flash point	<i>In vitro</i> cytogenicity (mammalian)	Abiotic degradation-hydrolysis as a function of pH
flammability	<i>In vitro</i> mutagenicity (mammalian)	Adsorption/desorption
explosive properties	Acute oral toxicity	Long-term toxicity to <i>Daphnia</i>
self-ignition temperature	Inhalation and/or dermal toxicity, as appropriate	Long-term toxicity to fish, ie one of the following
oxidising properties	Repeated dose toxicity - 28 d	<i>Either</i> : Fish early life stage toxicity
granulometry	Repeated dose toxicity - 90 d, if necessary	<i>or</i> Fish embryo and sac-fry acute toxicity
Stability/degradation products in organic solvents	Reproductive toxicity	<i>or</i> Juvenile fish growth
Dissociation constant	Toxicokinetic behaviour	Degradation testing (surface water, soil, sediment) if required
Viscosity	In vivo genotoxicity tests (if Annex V or VI studies give positive results)	Identification of degradation products

	Repeated dose toxicity 28 d, if not already provided	Bioaccumulation in fish (if required)
	Sub-chronic (90-day) toxicity (if necessary)	Further adsorption/desorption studies (if required)
	Pre-natal developmental toxicity (one species)	Effects on terrestrial organisms (if appropriate)
	Two-generation reproductive toxicity	<i>Depending on results</i>
	<i>Depending on results</i>	Confirmatory testing on biodegradation
	Long-term repeated toxicity (12 months)	Further information on the environmental fate and behaviour of the substance and/or degradation products
	Studies related to particular concerns	Effects on terrestrial organisms (long-term toxicity for earthworm, other soil invertebrates, and plants)
	Reproductive toxicity	Long-term toxicity to sediment organisms
	Two-generation reproductive toxicity	Long-term or reproductive toxicity to birds
	Carcinogenicity study	

## Rules for adaptation relating to physicochemical properties, 1000 tonnes

### Annex V

#### 7. INFORMATION ON THE PHYSICO-CHEMICAL PROPERTIES OF THE SUBSTANCE

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
7.1. State of the substance at 20°C and 101,3 kPa	
7.2. Melting/freezing point	7.2. The study does not need to be conducted below a lower limit of -20 °C.
7.3. Boiling point	7.3. The study does not need to be conducted: <ul style="list-style-type: none"> <li>– for gases; or</li> <li>– for solids which either melt above 300 °C or decompose before boiling. In such cases the boiling point under reduced pressure may be estimated or measured; or</li> <li>– for substances which decompose before boiling (e.g. auto-oxidation, rearrangement, degradation, decomposition, etc.).</li> </ul>
7.4. Relative density	7.4.:The study does not need to be conducted if <ul style="list-style-type: none"> <li>– the substance is only stable in solution in a particular solvent and the solution density is similar to that of the solvent. In such cases, an indication of whether the solution density is higher or lower than the solvent density is sufficient; or</li> <li>– the substance is a gas. In this case, an estimation based on calculation shall be made from its molecular weight and the Ideal Gas Laws.</li> </ul>
7.5. Vapour pressure	7.5. The study does not need to be conducted if the melting point is above 300 °C. If the melting point is between 200 °C and 300 °C, a limit value based on measurement or a recognised calculation method is sufficient.
7.6. Surface tension	7.6. The study need only be conducted if: <ul style="list-style-type: none"> <li>– based on structure, surface activity is expected or can be predicted; or</li> <li>– surface activity is a desired property of the material.</li> </ul> If the water solubility is below 1 mg/l at 20 °C the test does not need to be conducted.
7.7. Water solubility	7.7. The study does not need to be conducted if: <ul style="list-style-type: none"> <li>– the substance is hydrolytically unstable at pH 4, 7 and 9 (half-life less than 12 hours); or</li> <li>– the substance is readily oxidisable in water.</li> </ul> If the substance appears "insoluble" in water, a limit test up to the detection limit of the analytical method shall be performed.
7.8 Partition coefficient n-octanol/water	7.8. The study does not need to be conducted if the substance is inorganic. If the test cannot be performed (e.g. the substance decomposes, has a high surface activity, reacts violently during the performance of the test or does not dissolve in water or in octanol, or it is not possible to obtain a sufficiently pure substance), a calculated value for log P as well as details of the calculation method shall be provided.

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
7.9. Flash-point	<p>7.9. The study does not need to be conducted if:</p> <ul style="list-style-type: none"> <li>- the substance is inorganic; or</li> <li>- the substance only contains volatile organic components with flash-points above 100 °C for aqueous solutions; or</li> <li>- the estimated flash-point is above 200 °C; or</li> <li>- the flash-point can be accurately predicted by interpolation from existing characterised materials.</li> </ul>
7.10. Flammability	<p>7.10. The study does not need to be conducted:</p> <ul style="list-style-type: none"> <li>- if the substance is a solid which possesses explosive or pyrophoric properties. These properties should always be considered before considering flammability; or</li> <li>- for gases, if the concentration of the flammable gas in a mixture with inert gases is so low that, when mixed with air, the concentration is all time below the lower limit; or</li> <li>- for substances which spontaneously ignite when in contact with air.</li> </ul>
7.11. Explosive properties	<p>7.11. The study does not need to be conducted if:</p> <ul style="list-style-type: none"> <li>- there are no chemical groups associated with explosive properties present in the molecule; or</li> <li>- the substance contains chemical groups associated with explosive properties which include oxygen and the calculated oxygen balance is less than -200; or</li> <li>- the organic substance or a homogenous mixture of organic substances contains chemical groups associated with explosive properties, but the exothermic decomposition energy is less than 500 J/g and the onset of exothermic decomposition is below 500 °C; or</li> <li>- for mixtures of inorganic oxidising substances (UN Division 5.1) with organic materials, the concentration of the inorganic oxidising substance is: <ul style="list-style-type: none"> <li>- less than 15 %, by mass, if assigned to UN Packaging Group I (high hazard) or II (medium hazard)</li> <li>- less than 30 %, by mass, if assigned to UN Packaging Group III (low hazard).</li> </ul> </li> </ul> <p>Note: Neither a test for propagation of detonation nor a test for sensitivity to detonative shock is required if the exothermic decomposition energy of organic materials is less than 800 J/g.</p>
7.12. Self-ignition temperature	<p>7.12. The study does not need to be conducted:</p> <ul style="list-style-type: none"> <li>- if the substance is explosive or ignites spontaneously with air at room temperature; or</li> <li>- for liquids non flammable in air, e.g. no flash point up to 200 °C; or</li> <li>- for gases having no flammable range; or</li> <li>- for solids, if the substance has a melting point &lt; 160 °C, or if preliminary results exclude self-heating of the substance up to 400 °C.</li> </ul>

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
7.13. Oxidising properties	7.13. The study does not need to be conducted if: <ul style="list-style-type: none"> <li>- the substance is explosive; or</li> <li>- the substance is highly flammable; or</li> <li>- the substance is an organic peroxide; or</li> <li>- the substance is incapable of reacting exothermically with combustible materials, for example on the basis of the chemical structure (e.g. organic substances not containing oxygen or halogen atoms and these elements are not chemically bonded to nitrogen or oxygen, or inorganic substances not containing oxygen or halogen atoms). The full test does not need to be conducted for solids if the preliminary test clearly indicates that the test substance has oxidising properties.</li> </ul> <p>Note that as there is no test method to determine the oxidising properties of gaseous mixtures, the evaluation of these properties must be realised by an estimation method based on the comparison of the oxidising potential of gases in a mixture with that of the oxidising potential of oxygen in air.</p>
7.14. Granulometry	7.14. The study does not need to be conducted if the substance is marketed or used in a non solid or granular form.

#### Annex IX

#### 7. INFORMATION ON THE PHYSICOCHEMICAL PROPERTIES OF THE SUBSTANCE

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
7.15. Stability in organic solvents and identity of relevant degradation products Only required if stability of the substance is considered to be critical.	7.15. The study does not need to be conducted if the substance is inorganic.
7.16. Dissociation constant	7.16. The study does not need to be conducted if: <ul style="list-style-type: none"> <li>- the substance is hydrolytically unstable (half-life less than 12 hours) or is readily oxidisable in water; or</li> <li>- it is scientifically not possible to perform the test for instance if the analytical method is not sensitive enough.</li> </ul>
7.17. Viscosity	

#### Rules for adaptation relating to toxicological information, 1000 tonnes

*In vivo testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided.*

## Annex VII

### 8. TOXICOLOGICAL INFORMATION

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
8.1. Skin irritation or skin corrosion	
The assessment of this endpoint shall comprise the following consecutive steps: (1) an assessment of the available human and animal data, (2) an assessment of the acid or alkaline reserve, (3) <i>in vitro</i> study for skin corrosion, (4) <i>in vitro</i> study for skin irritation.	8.1. Steps 3 and 4 do not need to be conducted if: – the available information indicates that the criteria are met for classification as corrosive to the skin or irritating to eyes; or – the substance is flammable in air at room temperature; or – the substance is classified as very toxic in contact with skin; or – an acute toxicity study by the dermal route does not indicate skin irritation up to the limit dose level (2000 mg/kg body weight).
8.2. Eye irritation The assessment of this endpoint shall comprise the following consecutive steps: (1) an assessment of the available human and animal data, (2) an assessment of the acid or alkaline reserve, (3) <i>in vitro</i> study for eye irritation.	8.2. Step 3 does not need to be conducted if: – the available information indicates that the criteria are met for classification as corrosive to the skin or irritating to eyes; or – the substance is flammable in air at room temperature;
8.3. Skin sensitisation The assessment of this endpoint shall comprise the following consecutive steps: (1) an assessment of the available human, animal and alternative data, (2) <i>In vivo</i> testing .	8.3. Step 2 does not need to be conducted if: – the available information indicates that the substance should be classified for skin sensitisation or corrosivity; or – the substance is a strong acid (pH < 2.0) or base (pH > 11.5); or – the substance is flammable in air at room temperature. The Murine Local Lymph Node Assay (LLNA) is the first-choice method for <i>in vivo</i> testing. Only in exceptional circumstances should another test be used. Justification for the use of another test shall be provided.
8.4. Mutagenicity 8.4.1. <i>In vitro</i> gene mutation study in bacteria	8.4. Further mutagenicity studies shall be considered in case of a positive result.
8.5. Acute toxicity	8.5. The study/ies do(es) not generally need to be conducted if: – the substance is classified as corrosive to the skin. The study need not be conducted if a study on acute toxicity by the inhalation route (8.5.2) is available.
8.5.1. By oral route	

## Annex VIII

## 8. TOXICOLOGICAL INFORMATION

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
<p>8.1. Skin irritation 8.1.1. In vivo skin irritation</p>	<p>8.1.1. The study does not need to be conducted if:</p> <ul style="list-style-type: none"> <li>- the substance is classified as corrosive to the skin or as a skin irritant; or</li> <li>- the substance is a strong acid (pH &lt; 2.0) or base (pH &gt; 11.5); or</li> <li>- the substance is flammable in air at room temperature; or</li> <li>- the substance is classified as very toxic in contact with skin; or</li> <li>- an acute toxicity study by the dermal route does not indicate skin irritation up to the limit dose level (2000 mg/kg body weight); or</li> </ul>
<p>8.2. Eye irritation 8.2.1. In vivo eye irritation</p>	<p>8.2.1. The study does not need to be conducted if:</p> <ul style="list-style-type: none"> <li>- the substance is classified as irritating to eyes with risk of serious damage to eyes; or</li> <li>- the substance is classified as corrosive to the skin and provided that the registrant classified the substance as eye irritant; or</li> <li>- the substance is a strong acid (pH &lt; 2.0) or base (pH &gt; 11.5); or</li> <li>- the substance is flammable in air at room temperature; or</li> </ul>
<p>8.4. Mutagenicity 8.4.2. <i>In vitro</i> cytogenicity study in mammalian cells  8.4.3. In vitro gene mutation study in mammalian cells, if a negative result in Annex VII, 8.4.1. and Annex VIII, 8.4.2.</p>	<p>8.4.2. The study does not usually need to be conducted</p> <ul style="list-style-type: none"> <li>- if adequate data from an <i>in vivo</i> cytogenicity test are available or</li> <li>- the substance is known to be carcinogenic category 1 or 2 or mutagenic category 1, 2 or 3.</li> </ul> <p>8.4.3. The study does not usually need to be conducted if adequate data from a reliable <i>in vivo</i> mammalian gene mutation test are available.</p> <p>8.4. Appropriate <i>in vivo</i> mutagenicity studies shall be considered in case of a positive result in any of the genotoxicity studies in Annex VII or VIII.</p>
<p>8.5. Acute toxicity</p>	<p>8.5. The study/ies do(es) not generally need to be conducted if:</p> <ul style="list-style-type: none"> <li>- the substance is classified as corrosive to the skin.</li> </ul> <p>In addition to the oral route (8.5.1), for substances other than gases, the information mentioned under 8.5.2 to 8.5.3 shall be provided for at least one other route. The choice for the second route will depend on the nature of the substance and the likely route of human exposure. If there is only one route of exposure, information for only that route need be provided.</p>
<p>8.5.2. By inhalation</p>	<p>8.5.2. Testing by the <u>inhalation route</u> is <u>appropriate</u> if exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.</p>
<p>8.5.3. By dermal route</p>	<p>8.5.3. Testing by the <u>dermal route</u> is <u>appropriate</u> if:</p> <ol style="list-style-type: none"> <li>(1) inhalation of the substance is unlikely; and</li> <li>(2) skin contact in production and/or use is likely; and</li> <li>(3) the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin.</li> </ol>
<p>8.6. Repeated dose toxicity</p>	<p>8.6.1. The short-term toxicity study (28 days) does not need to be conducted if:</p>

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
<p>8.6.1. Short-term repeated dose toxicity study (28 days), one species, male and female, most appropriate route of administration, having regard to the likely route of human exposure.</p>	<ul style="list-style-type: none"> <li>- a reliable sub-chronic (90 days) or chronic toxicity study is available, provided that an appropriate species, dosage, solvent and route of administration were used; or</li> <li>- where a substance undergoes immediate disintegration and there are sufficient data on the cleavage products; or</li> <li>- relevant human exposure can be excluded in accordance with Annex XI (3).</li> </ul> <p>The appropriate route shall be chosen on the following basis:</p> <p><i>Testing by the dermal route is appropriate if:</i></p> <ul style="list-style-type: none"> <li>(1) inhalation of the substance is unlikely; and</li> <li>(2) skin contact in production and/or use is likely; and</li> <li>(3) the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin.</li> </ul> <p>Testing by the <u>inhalation route</u> is <u>appropriate</u> if exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.</p> <p>The <b>sub-chronic toxicity study</b> (90 days) (Annex IX, 8.6.2) shall be proposed by the registrant if: the frequency and duration of human exposure indicates that a longer term study is appropriate; and one of the following conditions is met:</p> <ul style="list-style-type: none"> <li>- other available data indicate that the substance may have a dangerous property that cannot be detected in a short-term toxicity study; or</li> <li>- appropriately designed toxicokinetic studies reveal accumulation of the substance or its metabolites in certain tissues or organs which would possibly remain undetected in a shortterm toxicity study but which are liable to result in adverse effects after prolonged exposure.</li> </ul> <p>Further studies shall be proposed by the registrant or may be required by the Agency in accordance with Article 39 or 40 in case of:</p> <ul style="list-style-type: none"> <li>- failure to identify a NOAEL in the 28 or the 90 days study, unless the reason for the failure to identify a NOAEL is absence of adverse toxic effects; or</li> <li>- toxicity of particular concern (e.g., serious/severe effects); or</li> <li>- indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation; In such cases it may also be more appropriate to perform specific toxicological studies that are designed to investigate these effects (e.g., immunotoxicity, neurotoxicity); or</li> </ul>
	<ul style="list-style-type: none"> <li>- the route of exposure used in the initial repeated dose study was inappropriate in relation to the expected route of human exposure and route-to-route extrapolation cannot be made; or</li> <li>- particular concern regarding exposure (e.g. use in consumer products leading to exposure levels which are close to the dose levels at which toxicity to humans may be expected ); or</li> <li>- effects shown in substances with a clear relationship in molecular structure with the substance being studied, were not detected in the 28 or the 90 days study.</li> </ul>
<p>8.7. Reproductive toxicity</p>	<p>8.7.1 This study does not need to be conducted if: the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented; or</p>

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
	<p>– the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented; or</p> <p>– relevant human exposure can be excluded in accordance with Annex XI (3); or</p> <p>– a pre-natal developmental toxicity study (8.7.2.) or a two-generation reproductive toxicity study (8.7.3.) is available.</p> <p>If a substance is known to have an adverse effect on fertility, meeting the criteria for classification as Repr Cat 1 or 2: R60, and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for development toxicity must be considered.</p> <p>If a substance is known to cause developmental toxicity, meeting the criteria for classification as Repr Cat 1 or 2: R61, and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered.</p>
<p>8.7.1. Screening for reproductive/developmental toxicity, one species (OECD 421 or 422), if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from in vitro methods that the substance may be a developmental toxicant.</p>	<p>In cases where there are serious concerns about the potential for adverse effects on fertility or development, either a pre-natal developmental toxicity study (Annex VII, 8.7.2.) or a two-generation reproductive toxicity study (Annex VII, 8.7.3.) may be proposed by the registrant instead of the screening study (8.7.1.).</p>
<p>8.8 Toxicokinetics</p> <p>8.8.1. Assessment of the toxicokinetic behaviour of the substance to the extent that can be derived from the relevant available information</p>	

## Annex IX

### 8. TOXICOLOGICAL INFORMATION

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
	<p>8.4. If there is a positive result in any of the in vitro genotoxicity studies in Annex VII or VIII and there are no results available from an in vivo study already, an appropriate in vivo somatic cell genotoxicity study shall be proposed by the registrant.</p> <p>If there is a positive result from an in vivo somatic cell study available, the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered.</p>

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
<p>8.6. Repeated dose toxicity  8.6.1. Short-term repeated dose toxicity study (28 days), one species, male and female, most appropriate route of administration, having regard to the likely route of human exposure, unless already provided as part of Annex VIII requirements or if tests according to 8.6.2 is proposed. In this case, Section 3 of Annex XI shall not apply</p>	
<p>8.6.2. Sub-chronic toxicity study (90-day), one species, rodent, male and female, most appropriate route of administration, having regard to the likely route of human exposure.</p>	<p>8.6.2. The sub-chronic toxicity study (90 days) does not need to be conducted if:</p> <ul style="list-style-type: none"> <li>– a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure; or</li> <li>– a reliable chronic toxicity study is available, provided that an appropriate species and route of administration were used; or</li> <li>– a substance undergoes immediate disintegration and there are sufficient data on the cleavage products (both for systemic effects and effects at the site of uptake); or</li> <li>– the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day "limit test", particularly if such a pattern is coupled with limited human exposure.</li> </ul> <p>The appropriate route shall be chosen on the following basis:</p> <p>Testing by the dermal route is appropriate if:</p> <ol style="list-style-type: none"> <li>(1) skin contact in production and/or use is likely; and</li> <li>(2) the physicochemical properties suggest a significant rate of absorption through the skin; and</li> <li>(3) one of the following conditions is met: <ul style="list-style-type: none"> <li>– toxicity is observed in the acute dermal toxicity test at lower doses than in the oral toxicity test; or</li> <li>– systemic effects or other evidence of absorption is observed in skin and/or eye irritation studies; or</li> <li>– in vitro tests indicate significant dermal absorption; or</li> <li>– significant dermal toxicity or dermal penetration is recognised for structurally-related substances.</li> </ul> </li> </ol> <p><i>Testing by the <u>inhalation</u> route is <u>appropriate</u> if:</i></p> <ul style="list-style-type: none"> <li>– exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.</li> </ul>

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
	<p>Further studies shall be proposed by the registrant or may be required by the Agency in accordance with Articles 39 or 40:</p> <ul style="list-style-type: none"> <li>- failure to identify a NOAEL in the 90 days study unless the reason for the failure to identify a NOAEL is absence of adverse toxic effects; or</li> <li>- toxicity of particular concern (e.g. serious/severe effects); or</li> <li>- indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation; In such cases it may also be more appropriate to perform specific toxicological studies that are designed to investigate these effects (e.g. immunotoxicity, neurotoxicity); or</li> <li>- particular concern regarding exposure (e.g. use in consumer products leading to exposure levels which are high relative to the dose levels at which toxicity to humans may be expected).</li> </ul>
8.7. Reproductive toxicity	<p>8.7. The studies do not need to be conducted if:</p> <ul style="list-style-type: none"> <li>- the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented; or</li> <li>- the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented; or</li> <li>- the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.</li> </ul> <p>If a substance is known to have an adverse effect on fertility, meeting the criteria for classification as Repr Cat 1 or 2: R60, and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for development toxicity must be considered.</p> <p>If a substance is known to cause developmental toxicity, meeting the criteria for classification as Repr Cat 1 or 2: R61, and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered.</p>
8.7.2. Pre-natal developmental toxicity study, one species, most appropriate route of administration, having regard to the likely route of human exposure (Annex X B.31 or OECD 414).	8.7.2. The study shall be initially performed on one species. A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data.
8.7.3. Two-generation reproductive toxicity study, one species, male and female, most appropriate route of	8.7.3. The study shall be initially performed on one species. A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
administration, having regard to the likely route of human exposure, if the 28-day or 90-day study indicates adverse effects on reproductive organs or tissues.	and all other relevant available data.

## Annex X

### 8. TOXICOLOGICAL INFORMATION

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN
	8.4. If there is a positive result in any of the in vitro genotoxicity studies in Annex VII or VIII, a second in vivo somatic cell test may be necessary, depending on the quality and relevance of all the available data. If there is a positive result from an in vivo somatic cell study available, the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered
8.6.3	8.6.3. A long-term repeated toxicity study ( $\geq 12$ months) may be proposed by the registrant or required by the Agency in accordance with Articles 39 or 40 if the frequency and duration of human exposure indicates that a longer term study is appropriate and one of the following conditions is met: – serious or severe toxicity effects of particular concern were observed in the 28 days or 90 days study for which the available evidence is inadequate for toxicological evaluation or risk characterisation; or – effects shown in substances with a clear relationship in molecular structure with the substance being studied were not detected in the 28 days or 90 days study; or – the substance may have a dangerous property that cannot be detected in a 90 days study
8.6.4	8.6.4 Further studies shall be proposed by the registrant or may be required by the Agency in accordance with Articles 39 or 40 in case of: – toxicity of particular concern (e.g. serious/severe effects); or – indications of an effect for which the available evidence is inadequate for toxicological evaluation and/or risk characterisation; In such cases it may also be more appropriate to perform specific toxicological studies that are designed to investigate these effects (e.g. immunotoxicity, neurotoxicity); or – particular concern regarding exposure (e.g. use in consumer products leading to exposure levels which are close to the dose levels at which toxicity is observed).
8.7. Reproductive toxicity	8.7. The studies need not be conducted if: – the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented; or – the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented; or – the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN
	substance in urine, bile or exhaled air) and there is no or no significant human exposure.
	<p>If a substance is known to have an adverse effect on fertility, meeting the criteria for classification as Repr Cat 1 or 2: R60, and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for development toxicity must be considered.</p> <p>If a substance is known to cause developmental toxicity, meeting the criteria for classification as Repr Cat 1 or 2: R61, and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered.</p>
8.7.2. Developmental toxicity study, one species, most appropriate route of administration, having regard to the likely route of human exposure (OECD 414).	
8.7.3. Two-generation reproductive toxicity study, one species, male and female, most appropriate route of administration, having regard to the likely route of human exposure, unless already provided as part of Annex IX requirements	
8.9.1 Carcinogenicity study	<p>8.9.1 A carcinogenicity study may be proposed by the registrant or may be required by the Agency in accordance with Articles 39 or 40 if:</p> <ul style="list-style-type: none"> <li>– the substance has a widespread dispersive use or there is evidence of frequent or long-term human exposure; and</li> <li>– the substance is classified as mutagen category 3 or there is evidence from the repeated dose study(ies) that the substance is able to induce hyperplasia and/or pre-neoplastic lesions.</li> </ul> <p>If the substances is classified as mutagen category 1 or 2, the default presumption would be that a genotoxic mechanism for carcinogenicity is likely. In these cases, a carcinogenicity test will normally not be required</p>

## Rules for adaptation relating to ecotoxicological information, 1000 tonnes

Annex VII

### 9. ECOTOXICOLOGICAL INFORMATION

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
<p>9.1. Aquatic toxicity</p> <p>9.1.1. Short-term toxicity testing on invertebrates (preferred species Daphnia)</p> <p>The registrant may consider long-term toxicity testing instead of short-term.</p>	<p>9.1.1. The study does not need to be conducted if:</p> <p>there are mitigating factors indicating that aquatic toxicity is unlikely to occur, for instance if the substance is highly insoluble in water or the substance is unlikely to cross biological membranes; or</p> <ul style="list-style-type: none"> <li>– a long-term aquatic toxicity study on invertebrates is available; or</li> <li>– adequate information for environmental classification and labelling is available.</li> </ul> <p>The long-term aquatic toxicity study on Daphnia (Annex IX, 9.1.5) shall be considered if the substance is poorly water soluble.</p>
<p>9.1.2. Growth inhibition study aquatic plants (algae preferred)</p>	<p>9.1.2. The study does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur for instance if the substance is highly insoluble in water or the substance is unlikely to cross biological membranes.</p>
<p>9.2. Degradation</p> <p>9.2.1. Biotic</p> <p>9.2.1.1. Ready biodegradability</p>	<p>9.2.1.1 The study does not need to be conducted if the substance is inorganic.</p>

Any other relevant physicochemical, toxicological and ecotoxicological information that is available shall be provided.

## Annex VIII

### 9. ECOTOXICOLOGICAL INFORMATION

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
<p>9.1.3. Short-term toxicity testing on fish: The registrant may consider long-term toxicity testing instead of short-term.</p>	<p>9.1.3. The study does not need to be conducted if:</p> <ul style="list-style-type: none"> <li>– there are mitigating factors indicating that aquatic toxicity is unlikely to occur, for instance if the substance is highly insoluble in water or the substance is unlikely to cross biological membranes; or</li> <li>– a long-term aquatic toxicity study on fish is available.</li> </ul> <p>Long-term aquatic toxicity testing as described in Annex IX shall be considered if the chemical safety assessment according to Annex I indicates the need to investigate further effects on aquatic organisms. The choice of the appropriate test(s) will depend on the results of the chemical safety assessment.</p> <p>The long-term aquatic toxicity study on fish (Annex IX, 9.1.6) shall be considered if the substance is poorly water soluble.</p>
<p>9.1.4. Activated sludge respiration inhibition testing</p>	<p>9.1.4. The study does not need to be conducted if:</p> <ul style="list-style-type: none"> <li>– there is no emission to a sewage treatment plant; or</li> <li>– there are mitigating factors indicating that microbial toxicity is unlikely to occur, for instance the substance is highly insoluble in water; or</li> <li>– the substance is found to be readily biodegradable and the applied test concentrations are in the range of</li> </ul>

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
	concentrations that can be expected in the influent of a sewage treatment plant. The study may be replaced by a nitrification inhibition test if available data show that the substance is likely to be an inhibitor of microbial growth or function, in particular nitrifying bacteria.
9.2. Degradation	9.2. Further degradation testing shall be considered if the chemical safety assessment according to Annex I indicates the need to investigate further the degradation of the substance. The choice of the appropriate test(s) will depend on the results of the chemical safety assessment.
9.2.2. Abiotic 9.2.2.1. Hydrolysis as a function of pH.	9.2.2.1. The study does not need to be conducted if: – the substance is readily biodegradable; or – the substance is highly insoluble in water.
9.3. Fate and behaviour in the environment 9.3.1. Adsorption/desorption screening	9.3.1. The study does not need to be conducted if: – based on the physicochemical properties the substance can be expected to have a low potential for adsorption (e.g. the substance has a low octanol water partition coefficient); or – the substance and its relevant degradation products decompose rapidly.

## Annex IX

### 9. ECOTOXICOLOGICAL INFORMATION

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
9.1. Aquatic toxicity  9.1.5. Long-term toxicity testing on invertebrates (preferred species <i>Daphnia</i> ), (unless already provided as part of Annex VII requirements) 9.1.6. Long-term toxicity testing on fish, (unless already provided as part of Annex VIII requirements) The information shall be provided for one of the sections 9.1.6.1, 9.1.6.2 or 9.1.6.3.	9.1. Long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. The choice of the appropriate test(s) depends on the results of the chemical safety assessment.
9.1.6.2. Fish early-life stage (FELS) toxicity 9.1.6.2. Fish short-term toxicity test on embryo and sac-fry stages 9.1.6.3. Fish, juvenile growth test	

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
9.2. Degradation	9.2. Further biotic degradation testing shall be proposed if the chemical safety assessment according to Annex I indicates the need to investigate further the degradation of the substance and its degradation products. The choice of the appropriate test(s) depends on the results of the chemical safety assessment and may include simulation testing in appropriate media (e.g. water, sediment or soil).
9.2.1. Biotic	
9.2.1.2. Simulation testing on ultimate degradation in surface water	9.2.1.2. The study need not be conducted if: – the substances is highly insoluble in water ; or – the substance is readily biodegradable.
9.2.1.3. Soil simulation testing (for substances with a high potential for adsorption to soil)	9.2.1.3. The study need not be conducted: – if the substance is readily biodegradable; or – if direct and indirect exposure of soil is unlikely.
9.2.1.4. Sediment simulation testing (for substances with a high potential for adsorption to sediment)  9.2.3. Identification of degradation products	9.2.1.4. The study need not be conducted: – if the substance is readily biodegradable; or – if direct and indirect exposure of sediment is unlikely. 9.2.3. Unless the substance is readily biodegradable
9.3. Fate and behaviour in the environment 9.3.2. Bioaccumulation in aquatic species, preferably fish  9.3.3. Further information on adsorption/desorption depending on the results of the study required in Annex VIII	9.3.2. The study need not be conducted if: – the substance has a low potential for bioaccumulation (for instance a log Kow < 3) and/or a low potential to cross biological membranes; or – direct and indirect exposure of the aquatic compartment is unlikely. 9.3.3. The study need not be conducted if: – based on the physicochemical properties the substance can be expected to have a low potential for adsorption (e.g. the substance has a low octanol water partition coefficient); or – the substance and its degradation products decompose rapidly.
9.4. Effects on terrestrial organisms	9.4. These studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely.

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
<p>9.4.1. Short-term toxicity to invertebrates            9.4.2. Effects on soil micro-organisms            9.4.3. Short-term toxicity to plants</p>	<p>In the absence of toxicity data for soil organisms, the equilibrium partitioning method may be applied to assess the hazard to soil organisms. The choice of the appropriate tests depends on the outcome of the chemical safety assessment.            In particular for substances that have a high potential to adsorb to soil or that are very persistent, the registrant shall consider long-term toxicity testing instead of short-term.</p>

### Annex X

STANDARD INFORMATION REQUIRED	SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
<p>9.2. Degradation</p> <p>9.2.1. Biotic</p>	<p>9.2. Further biotic degradation testing shall be proposed if the chemical safety assessment according to Annex I indicates the need to investigate further the degradation of the substance and its degradation products. The choice of the appropriate test(s) depends on the results of the chemical safety assessment and may include simulation testing in appropriate media (e.g. water, sediment or soil).</p>
<p>9.3. Fate and behaviour in the environment            9.3.4. Further information on the environmental fate and behaviour of the substance and/or degradation products</p>	<p>9.3.4 Further testing shall be proposed by the registrant or may be required by the Agency in accordance with Article 39 or 40 if the chemical safety assessment according to Annex I indicates the need to investigate further the fate and behaviour of the substance. The choice of the appropriate test(s) depends on the results of the chemical safety assessment.</p>

9.4. Effects on terrestrial organisms	9.4. Long-term toxicity testing shall be proposed by the registrant if the results of the chemical safety assessment according to Annex I indicates the need to investigate further the effects of the substance and/or degradation products on terrestrial organisms. The choice of the appropriate test(s) depends on the outcome of the chemical safety assessment. These studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely.
9.4.4. Long-term toxicity testing on invertebrates , unless already provided as part of Annex VII requirements. 9.4.6. Long-term toxicity testing on plants, unless already provided as part of Annex VII requirements.	
9.5.1. Long-term toxicity to sediment organisms	9.5.1. Long-term toxicity testing shall be proposed by the registrant if the results of the chemical safety assessment indicates the need to investigate further the effects of the substance and/or relevant degradation products on sediment organisms. The choice of the appropriate test(s) depends on the results of the chemical safety assessment.
9.6.1. Long-term or reproductive toxicity to birds	9.6.1. Any need for testing should be carefully considered taking into account the large mammalian dataset that is usually available at this tonnage level.

### **Data requirements at 1 - 10 tonnes per annum**

Annex VII details the testing requirements for production and import volumes of one tonne or more.

Physicochemical properties required include:

- Physical state of substance at 20°C and 1014 hPa
- Melting/freezing point
- Relative density
- Vapour pressure
- Surface tension
- Water solubility
- Partition coefficient n-octanol/water

Additionally, where appropriate, flash point, flammability, explosive properties, self-ignition temperature, oxidising properties and granulometry are required.

Toxicological endpoints that should be assessed using existing data and *in vitro* data are:

- Skin irritation/corrosivity
- Eye irritation
- Skin sensitisation
- Mutagenicity
- Acute oral toxicity

The ecotoxicity information required is:

- Short-term (or long-term) toxicity to Daphnia
- Algal growth inhibition
- Biotic degradation
- Ready biodegradability

It has been suggested that these test requirements should be revised before 2011, after which date existing substances of this tonnage should be registered.

### **Data requirements at 10 - 100 tonnes per annum**

The additional data requirements at this level, in AnnexVIII, include:

Toxicological data

- In vivo* tests for skin irritation and eye irritation (not required for corrosive substances, nor if hazardous effects identified in *in vitro* tests)
- Bacterial and mammalian *in vitro* mutagenicity tests
- Mammalian *in vitro* cytogenicity test
- Inhalation and/or dermal toxicity, as appropriate
- Repeated dose toxicity 28 d (90 d if necessary)
- Reproductive toxicity
- Toxicokinetic behaviour

Ecotoxicological requirements at this level include:

- Fish short-term toxicity
- Activated sludge respiration inhibition test
- Further degradation studies (if a need is indicated in chemical safety assessment)
- Abiotic degradation-hydrolysis as a function of pH
- Adsorption/desorption.

### **Data requirements at 100 - 1000 tonnes per annum**

Further requirements are:

Physicochemical properties:

- Stability/degradation products in organic solvents
- Dissociation constant
- Viscosity

Toxicological data

- In vivo* mutagenicity tests (if Annex VII or VIII studies give positive results)
- Repeated dose toxicity
- Repeat dose (28-day) toxicity (if not already provided)
- Sub-chronic (90-day) toxicity (if necessary)
- Developmental toxicity (two species)
- Two-generation reproductive toxicity (if indicated by sub-chronic tests)

## Ecotoxicological studies

- Long-term toxicity to *Daphnia*
- Long-term toxicity to fish, ie one of:
  - Fish early life stage toxicity
  - Fish embryo and sac-fry toxicity
  - Juvenile fish growth
- Degradation testing (surface water, soil, sediment) if required
- Identification of degradation products
- Bioaccumulation in fish (if required)
- Further adsorption/desorption studies (if required)
- Effects on terrestrial organisms (if appropriate)

## **Data requirements above 1000 tonnes per annum**

Annex X details additional requirements for high production volumes. Requirement for additional tests depend upon results of the tests required by Annexes VII, VIII and IX. Application of Annex X might lead to the need for additional tests. These are:

### Toxicological data

- Long-term repeated toxicity (12 months)
- Studies related to particular concerns
- Two-generation reproductive toxicity
- Carcinogenicity study

### Environmental and ecotox data

- Confirmatory testing on biodegradation
- Fate and behaviour in the environment of substance and/or degradation products
- Effects on terrestrial organisms (long-term toxicity for earthworm, other soil invertebrates, and plants)
- Long-term toxicity to sediment organisms
- Long-term or reproductive toxicity to birds