



Nordic Project on Information Strategies (NOIS) for Fulfilling Data Requirements under REACH

Part 1 - Review of Current Testing/Information
Requirements

June 2005

Nordic Project on Information Strategies (NOIS) for Fulfilling Data Requirements under REACH

Part 1 - Review of Current Testing/Information Requirements

ANP 2005:754

© Nordic Council of Ministers, Copenhagen 2005

ISBN 92-893-1193-2

This publication can be ordered on www.norden.org/order. Other Nordic publications are available at www.norden.org/publications

Nordic Council of Ministers

Store Strandstræde 18
DK-1255 Copenhagen K
Phone (+45) 3396 0200
Fax (+45) 3396 0202

Nordic Council

Store Strandstræde 18
DK-1255 Copenhagen K
Phone (+45) 3396 0400
Fax (+45) 3311 1870

www.norden.org

Nordic Environmental Co-operation

Environmental co-operation is aimed at contributing to the improvement of the environment and forestall problems in the Nordic countries as well as on the international scene. The co-operation is conducted by the Nordic Committee of Senior Officials for Environmental Affairs. The co-operation endeavours to advance joint aims for Action Plans and joint projects, exchange of information and assistance, e.g. to Eastern Europe, through the Nordic Environmental Finance Corporation (NEFCO).

Nordic co-operation

Nordic co-operation, one of the oldest and most wide-ranging regional partnerships in the world, involves Denmark, Finland, Iceland, Norway, Sweden, the Faroe Islands, Greenland and Åland. Co-operation reinforces the sense of Nordic community while respecting national differences and similarities, makes it possible to uphold Nordic interests in the world at large and promotes positive relations between neighbouring peoples.

Co-operation was formalised in 1952 when *the Nordic Council* was set up as a forum for parliamentarians and governments. The Helsinki Treaty of 1962 has formed the framework for Nordic partnership ever since. The *Nordic Council of Ministers* was set up in 1971 as the formal forum for co-operation between the governments of the Nordic countries and the political leadership of the autonomous areas. i.e. the Faroe Islands, Greenland and Åland.

Content

Preface	7
Environment	9
1. Introduction to Environmental Endpoints	9
2. Background and Objective	9
2.1 Background.....	9
2.2 Objective.....	9
3. Methods	10
4. Results and Discussion.....	11
4.1 Volume.....	11
4.2 Hazard and other Intrinsic Properties.....	13
4.3 Risk or Exposure (Potential Risk)	15
4.4 Other Factors.....	18
5. Conclusions	18
Human Health.....	21
6. Introduction to Human Health Endpoints	21
7. Objective	22
8. Elements of the Information Strategies	22
8.1 Use of Existing Data	22
8.2 (Q)SAR	23
8.3 Read Across	23
8.4 In Vitro Tests	23
8.5 In Vivo Tests	24
8.6 Exposure Driven Testing.....	24
9. Inventory and Comparison of Existing Information Strategies and Criteria for Classification	26
9.1 Acute Toxicity	26
9.2 Irritation / Corrosion	31
9.3 Toxicity to Reproduction and Development	35
10. Conclusions on Human Health Endpoints.....	44
References	51
Appendix A Overview of Environmental Test Requirements or Needs under Various Legislation	53
Appendix B Overview of Human Health Test Requirements or Needs under Various Legislation	59

Preface

In 2004 the EU Commission initiated several activities for development of technical guidance documents in support of the new EU Chemicals Legislation (REACH). These REACH Implementation Projects (RIP) focus on many aspects of REACH.

A Nordic project on information strategies (NOIS) was started in order to produce quick and early input to the REACH Implementation Project on information strategies (RIP 3.3).

The REACH proposal contains testing requirements that are mainly dependent on production volumes. To get a practical system, additional guidance is needed on how to obtain the necessary information (by using intelligent sequences of testing), how to use different kinds of information, how to make decisions based on different types of data (e.g., when to stop testing and/or take action). The guidance could be produced by elaboration of testing or information strategies (including the use of QSAR, grouping, read across, in vitro and in vivo data, and release/exposure related information), with data generation in a stepwise approach, where, in principle, a higher level would correspond to more relevant, certain and accurate data. Thus, the implementation of the REACH proposal requires development of Integrated Information Strategies (IIS), that will assist in designing testing programs that give useful information while still being animal- and resource saving.

In this project, the aim is to prepare information strategies that can be used as a basis for the development of REACH guidance documents. The project is divided in two parts, where a review of currently used testing or information strategies (including a comparison with the REACH requirements) is done first (part 1), followed by development of IISs for individual endpoints (part 2). As it is a very big task to cover all endpoints, only selected environmental and human health endpoints are covered. This report contains the review (part 1), and part 2 will be published later.

This report has been prepared by consultants under a contract with the Nordic Chemicals Group of the Nordic Council of Ministers. The environmental part has been written by Finn Pedersen (DHI Water and Environment, Denmark), and the human health part by Kimmo Louekari (The Finnish Institute of Occupational Health) and Ulla Hass (The Danish Institute for Food and Veterinary Research, DFVF). The work has been guided by a Nordic Steering group, with the following members from the Nordic authorities: Alicja Andersson, Gunilla Eriksson, Bert-Ove Lund, Katarina Lundberg and Ivar Lundbergh representing the Swedish Chemicals Inspectorate (KemI), Sweden; Gunnlaug Einarisdóttir representing

the Environment & Food Agency (UST), Iceland; Jaana Heiskanen representing the Finnish Environment Institute (SYKE), Finland; Marko Kuitinen and Kirsi Sihvonen representing the National Product Control Agency for Welfare and Health (STTV), Finland; Lotte Kau Anderson and Henrik Tyle representing the Danish Environmental Protection Agency (MST), Denmark; Toralf Kaland and Vibeke Sømnes representing the Norwegian Pollution Control Authority (SFT), Norway. The steering group, as well as other colleagues at the Nordic authorities have provided valuable information and input to the work. The Swedish Chemicals Inspectorate has acted as lead for the project.

Environment

1. Introduction to Environmental Endpoints

The Nordic Chemicals Group (NKG) under the Nordic Council of Ministers has initiated the project “Elaboration of testing strategies for effect assessment under REACH”. Part 1 of this project comprises a review and an assessment of existing testing strategies, and chapters 1-6 of the current report deals with the environmental part.

2. Background and Objective

2.1 Background

By 29 October 2003, the European Commission launched its proposal for a new chemical legislation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Future data requirements for all substances are specified in the Annexes IV to IX to the REACH proposal. This information strategy builds on and tends to integrate and merge current strategies that are available for existing and new industrial chemicals in the EU and OECD and to some extent also information strategies for biocides and pesticides. It is the intention that the information strategy given in the REACH proposal will be further specified and detailed in a guidance document, which will be developed in the so-called REACH Implementation Project No. 3.3 on “Guidance on information requirements”, which will be funded by the European Commission.

The Nordic countries, at several meetings sponsored by NKG, have identified a mutual interest in contributing to the work on implementing REACH within the fields of information strategies as elaboration of testing strategies (including the use of QSAR, grouping, read across, and release/exposure related information) has the highest priority for these countries. The current project, therefore, intends to feed into both the RIP-3.3 project, which will be launched shortly, and the council negotiations on the REACH proposal.

2.2 Objective

The objective of part 1 of the project is to obtain a sufficient overview of existing information and testing strategies for identifying endpoints or

groups of endpoints for which further criteria or guidance for fulfilment of information requirements may be developed as examples of useful integrated information strategies. This will primarily be used as the background for a step 2 of the current project and/or as input to the RIP-3.3 project.

3. Methods

Part 1 comprises a review and an assessment of the information and testing strategies that pertain to various regulatory schemes. For each regulatory scheme in force, various guidance documents are available regarding, i.e., for which endpoints data have to be available and/or submitted and under which conditions information is required or may be omitted. The following regulatory schemes and guidance documents have been reviewed¹:

- REACH proposal, Annexes IV to IX
- guidance in Annexes V to IX
- Existing Substances Regulation, Annexes III and IV (ESR)
- guidance in the TGD (EC 2003)
- New substances, Council directive 67/548/EEC, Annex VII (NONS)
- guidance in Manual of Decisions (ECB 2004) and in the TGD (EC 2003)
- Classification & labelling,
- Council directive 67/548/EEC, Annex VI (C&L)
- Globally Harmonised System (GHS) (UN 2003)
- PBT/vPvB assessment guidance in the TGD (EC 2003) (slightly expanded in the REACH proposal, but not considered here)
- Biocidal Products Directive, Annexes IIA and IIIA (BPD)
- guidance in Technical Notes for Guidance on data requirements (EC 2000)
- Plant Protection Products Directive, Annex II (PPP)
- guidance in Annex II
- guidance document on aquatic ecotoxicology (DG SANCO 2002a)
- guidance document on terrestrial ecotoxicology (DG SANCO 2002b)
- OECD: Manual for investigation of HPV chemicals

The project is conducted as a comparative review of information requirements regarding environmental hazard of chemicals under various regulatory schemes (as described in various working and guidance docu-

¹ Note that no testing strategies are found in Directive 1999/45/EEC, the GHS system (OECD 2001 & UN 2003) and the JRC document on testing needs under REACH (Pedersen et al. 2003). In stead the testing strategies under the biocides and pesticides directives are included. The ECVAM publication (Combes et al. 2003) deals with general considerations on human health and is not reviewed here.

ments relating to current legislation and/or REACH) and their dependence on volume, hazard, risk or other trigger factors.

4. Results and Discussion

An overview of testing requirements under various regulatory schemes is given in Appendix A as well as a short description of the specific conditions, which trigger the need for information about each of the various environmental endpoints. The different conditions are presented and discussed in detail in the text below.

4.1 Volume

Under current legislation, volume (or quantity) of a substance manufactured or imported and marketed in the EU is in itself used only as a trigger for requiring data on a specific endpoint under the notification of new substances (NONS) scheme. The scheme comprises all substances, which were not placed on the market during a 10-year period prior to 1981. For new substances placed on the market in a quantity of > 1 tonne per year per manufacturer or importer, “base set” data are required, but with increasing volume also an increasing amount of information is required². Thus, this approach takes into account various aspects; (i) that in average, increasing volume would result in increased exposure and thus an anticipated increased risk to human health and the environment, (ii) that marketing of a new substance would normally start with a small volume which eventually may increase with time, and (iii) that an increase in the marketed volume would normally generate an increased profit, which would allow the funding of more data.

The ESR programme is different from the NONS scheme, as it is dealing with existing substances that are already manufactured or imported and placed on the market in the EU. The EU ESR programme consists of three steps, i.e. (i) priority setting of High Production Volume Chemicals, (ii) risk assessment and (iii) risk management. Thus, again assuming that in average, the biggest risks could be expected for substances marketed in the highest volumes, these two programmes have started their evaluations with those substances that are manufactured or imported in volumes of more than 1,000 tonnes per year per manufacturer or importer. For the almost 3,000 substances manufactured or imported in the EU, available information on intrinsic properties was requested in the ESR to be submitted (now available in the IUCLID database). For prioritised sub-

² The tonnage trigger for requiring Level 1 testing is 100 tonnes per year (at 10 t parts of level 1 may be required) and for Level 2 testing is 1000 tonnes per year. Note also that less information than in base set is required already at 10 and 100 kg per year.

stances undergoing risk assessment at least the “base set” data³ are required and hence, if certain base set data are not available, such data has to be provided by the manufacturer or importer. Such data may concern exposure information or generation of new test data concerning intrinsic properties of the substance, including hazardous properties. Furthermore, in the EU additional information may, if there is a concern in relation to risk, be requested by the rapporteur Member State and endorsed by the Article 15 Committee. Thus, contrary to the NONS scheme the tonnage trigger does not specify the amount of data required, but only the group of substances among which the 141 substances have been prioritised for risk assessment. For these, risk assessment have in December 2004 been completed or almost completed for approximately 100 substances since the programme started in 1995.

A similar High Production Volume Chemicals programme (the SIDS programme) exists in the OECD to which the EU ESR programme feeds in. The SIDS programme concerns chemicals produced in quantities > 1000 tonnes per year per manufacturer in at least two OECD regions (North America, Europe, Asia). The SIDS programme has focus on obtaining the base set of test data on the HPV chemicals. It includes an initial hazard assessment supplemented with limited exposure information and no risk management step, but only a general recommendation on the need for further work. The SIDS programme has the ambition to provide assessments on all HPVCs and does not require further test data beyond the base set. IN December 2004 the SIDS programme has concluded assessment on about 500 substances (as such or as part of categories of substances) since it started in 1985. The number of substances assessed each year has increased significantly in later years, mainly due to an industry programme (the ICCA programme) feeding into the SIDS programme.

The legislation on biocides and pesticides is fundamentally different from the legislation on industrial chemicals. First of all, these substances are used because of their biological activity, as it is the intention that these substances shall exert a controlling effect on harmful organisms with the purpose of protecting beneficial plants, animals or physical structures. Therefore, due to the intended biological activity of these substances, it has been decided that it is necessary that authorities approve the marketing and use of these substances in order to prevent unacceptable risks to human health or the environment. In order to assess the potential risks to human health and the environment, comprehensive data requirements have been decided. The requirements are independent of the volume of the substances that is manufactured or imported, but depend on the intended use and/or the intrinsic hazards of the substances.

³ The base set of test data is required only in the EU. In the USA, no base set test data is needed. Instead SAR, QSAR and other information may be used – and only when US EPA has identified an unreasonable risk, new test data from the importer or manufacturer is demanded.

In conclusion, in current regulatory schemes the manufactured or imported volume of a substance is used for defining the data requirement for new substances, while it has no influence on the data requirements for existing substances, biocides and pesticides. This is due to the fundamental differences between the various types of legislation and review programmes and, therefore, it is not relevant to compare the use of volume for triggering data requirements.

The proposed REACH Regulation is intended to replace both the NONS and the ESR system in the EU. In future, data will be required for all of the estimated 30,000 existing substances on the market in quantities above 1 tonne per year. Under the ESR only already available information was required to be submitted to the IUCLID database for the about 2,700 substances manufactured or imported in quantities above 1,000 tonnes per year. For the 140 prioritised existing substances information corresponding to the so-called "base set" was actually required if not available.

In the REACH proposal, it is argued that "requirements for generation of information on substances should be tiered according to the volume of manufacture or importation of a substance, because these provide an indication of the potential for exposure of man and the environment to the substances"⁴. Thus, the REACH proposal takes over the basic principles of NONS with the volume as the driving factor for determining the information requirements. However, it has also been recognised in the White Paper on a future chemicals policy that the burdens of fulfilling the data requirements under NONS for substances manufactured or imported in low volumes are so high that innovation has been hindered (EC 2001). Therefore, REACH tends to integrate the two current systems into one system with intermittent data requirements with volume still being the main trigger for requiring data for the individual endpoints. However, under REACH data requirements will be considerably more lenient than for new substances under the current system, e.g., for most endpoints of the base set, the tonnage trigger is a factor 10 higher under REACH than for new substances.

4.2 Hazard and other Intrinsic Properties

In information and testing strategies, information about a specific endpoint may be needed, if a substance has a certain hazard or another intrinsic property, or the information may be waived if a certain property demonstrates that the information is not necessary. In general, this pertains to the need for information regarding the fate and behaviour of certain groups of substances.

⁴ REACH proposal, preamble paragraph 24.

For notification of new substances (NONS), the Manual of Decisions established between the Commission and the Competent Authorities after the 51th meeting of Competent Authorities (Rome, 1996) specifies that the testing requirements at level 1 and level 2 should be decoupled from the results of the risk assessment (EC 2004). In principle, this would mean that exemptions from level 1 and 2 tests should be based on the outcome of earlier tests, i.e. intrinsic properties, but rarely the outcome of a risk assessment. However, further data requirement can, aside from the reaching of a higher tonnage level, also be triggered by the outcome of a risk assessment as well as intrinsic properties. (See also comments in section 4.3). One example of a situation where a hazard would trigger further information is the need for supplementary degradation studies (e.g. simulation of degradation in surface water, sediment or soil), if sufficient degradation has not been proved in a test for ready biodegradability. Also, Hydrolysis is normally required if a substance is not readily biodegradable. Before a biodegradation test is carried out, a test for bacterial inhibition may be needed, if biodegradation may be affected. However, the latter is implicitly the case under other assessment schemes as well, although it is not specified in the various guidance documents.

In the EU ESR programme no information needs are based on intrinsic (hazardous) properties. However, under the OECD HPVC programme the need for a hydrolysis test is determined on the basis of the chemical structure of the substance with a structure resistant to hydrolysis a justification for waiving this test.

For biocides, degradation products will have to be identified for substances that are not readily biodegradable. For pesticides such identification shall always be conducted as part of a soil degradation study.

Substances shall be classified on the basis of their intrinsic properties (Council Directive 92/32/EEC). Formally, classification is based on available information and as such, no testing is required. However, a data generation strategy is an implicit part of the classification criteria in particular in relation to the use of additional data when base set data suggest the need for classifying a substance. One example is the use of experimentally derived information on the bioconcentration factor to overrule the estimated bioaccumulation potential from the octanol-water partitioning coefficient ($\log P_{ow}$). Another example is the criteria for declassifying chemicals by documentation of a proven potential to degrade rapidly in the aquatic environment and/or the absence of chronic aquatic toxicity at 1 mg/L or the solubility limit. The same principles apply to the Globally Harmonized System where it is stated explicitly that “the GHS itself does not include requirements for testing” (§1.3.2.4.1, UN 2003).

The PBT assessment is described in the TGD on risk assessment (EC 2003) as a two-step process with the first step being the identification of PBT substances based on criteria on intrinsic properties and the second an evaluation of sources, emissions and pathways. The starting point for the

assessment is that screening data on biodegradation, bioaccumulation and toxicity indicate that a substance is a potential PBT or vPvB substance. The testing strategy for a further clarification on whether or not the substance fulfils the criteria has been elaborated in which the use of animal tests as far as possible is avoided. Therefore, the strategy starts with studies on persistence in order to clarify the fulfilment of the P criterion and only if this is fulfilled, should further testing be conducted. The next step would then be tests for clarifying the B criterion and as a final step, could the T criterion be elucidated. The PBT assessment is also part of the REACH proposal in a slightly expanded version.

In contrast to the rather scarce specifications on information needs in current legislation (but more extensively in various guidance documents) depending on intrinsic (hazardous) properties, such information requirements have been defined in the REACH proposal in the legal text in a significantly more detailed level:

- **Aquatic toxicity:** Information on acute aquatic toxicity is not required for substances that are highly insoluble ($S_w < 10 \mu\text{g/L}$) and, in stead, a long-term aquatic toxicity test shall be considered. Aquatic toxicity tests are not needed or can be waived for substances that are unlikely to cross biological membranes ($MW > 800 \text{ g/mol}$ or molecular diameter $> 15 \text{ \AA}$). Also a test on activated sludge respiration inhibition may be waived for substances that are highly insoluble or that are readily biodegradable. A test on nitrification inhibition may be required for substances that are inhibitors to microbial activity.
- **Degradation:** Information on biodegradation is not needed for inorganic substances. For readily biodegradable substances, degradation simulation tests and identification of degradation products are not needed and neither is information on hydrolysis. For highly insoluble substances ($S_w < 10 \mu\text{g/L}$), information on degradation in aquatic environments is not required.
- **Fate and behaviour:** Information on the n-octanol/water partitioning ($\log P_{ow}$) is not needed for inorganics. An adsorption/desorption study is not needed if based on physicochemical properties, the substance has a low potential for sorption or if it decomposes rapidly. A bioconcentration test is not required for substances that have a low potential for bioaccumulation ($\log P_{ow} < 3$) or are unlikely to cross biological membranes ($MW > 800 \text{ g/mol}$ or molecular diameter $> 15 \text{ \AA}$).

4.3 Risk or Exposure (Potential Risk)

When a potential risk to, or a likely exposure of, a certain environment or group of organisms has been identified, further information may be needed for elucidating the possible impact. Such obligations have been

specified at various levels in the regulatory schemes that are reviewed here.

For notification of new substances, the Commission Directive 93/67/EEC on principles for risk assessment specifies that, depending on the risk or potential risk identified in a risk assessment, it may be concluded that further information shall be requested. This pertains to two of the possible four conclusions, i.e. conclusion (ii) that “the substance is of concern and the competent authority shall decide what further information is required for revision of the assessment but shall defer a request for that information until the quantity placed on the market reaches the next tonnage threshold”, and conclusion (iii) that “the substance is of concern and further information shall be requested immediately” (Commission Directive 1993).

For existing substances long-term aquatic toxicity tests may be required if a risk has been identified and there is a need to refine the Predicted No-Effect-Concentration (PNEC) for the aquatic environment. In general, the test should be conducted with the organism showing the highest sensitivity in short-term toxicity tests. Studies simulating the biodegradation in the environment may be requested for environments (e.g. sewage treatment plant, surface water, sediment, soil) for which information on degradation rates would improve the assessment. Tests concerning toxicity to terrestrial organisms are required if a potential risk has been identified by extrapolating from aquatic toxicity data by use of the equilibrium partitioning approach. Further long-term terrestrial toxicity tests may then be needed for revising the PNEC for soil derived from short-term toxicity data. Finally, studies on long-term toxicity to sediment organisms may be required when a risk has been identified by extrapolating from short-term test data on sediment organisms or from aquatic test data by use of the equilibrium partitioning approach.

The core data requirements for both biocides and pesticides are in general much higher than for industrial chemicals; however they are also much more flexible with potential exposure and risk among the driving factors. The information described below is needed for both types of chemicals unless where specified. Activated sludge respiration inhibition tests may be needed when the use of the substance may result in discharge to the sewage system and adverse effects on the STP. Information on long-term aquatic toxicity is needed when exposure of the aquatic environment is likely. Studies on simulation of degradation processes are required for those environmental compartments that are likely to be exposed. This pertains to surface water, sediment and soil (only pesticides), phototransformation in air, active sludge (only biocides), biodegradation in seawater (only biocides, in particular antifouling biocides) and the anaerobic environment. For pesticides, an adsorption/desorption study is not required if there is no exposure of the soil compartment. Further studies of fate and behaviour (incl. adsorption/desorption, mobility in soil)

may be needed for biocides when a risk to soil or groundwater has been identified. Studies on bioconcentration in fish are needed for lipophilic pesticides ($\log Pow > 3$) unless exposure is unlikely or there is a high depuration rate. Short-term terrestrial toxicity data are needed if the soil compartment is likely to be exposed, and if a long-term exposure and risk is anticipated long-term toxicity studies with terrestrial organisms may be requested for pesticides. Toxicity studies with honeybees and other so-called “beneficial arthropods” are needed for pesticides if exposure is likely and the same is the case for studies with birds. Also long-term sediment toxicity tests may be required for pesticides when exposure and toxicity to sediment dwelling organisms is likely.

The information strategy described in the REACH proposal uses potential exposure and risk for triggering or waiving the need for data for some endpoints for which information is required when the manufactured or imported quantity exceeds 100 or 1,000 tonnes per year:

- **Aquatic toxicity:** Long-term aquatic toxicity tests are not needed if direct or indirect exposure of the aquatic environment is unlikely.
- **Degradation:** The need for studies on simulation of biodegradation in soil or sediment depends on the outcome of the chemical safety assessment, but data will not be required if direct or⁵ indirect exposure is unlikely. The need for further confirmation of biodegradation rates and identification of degradation products will depend on the results of the safety assessment.
- **Fate and behaviour:** A study on bioconcentration in fish may be waived if direct or⁶ indirect exposure of the aquatic environment is unlikely. Further fate and behaviour studies shall be proposed depending on the results of the safety assessment.
- **Terrestrial toxicity:** Short-term toxicity studies with terrestrial organisms are not needed if direct or⁷ indirect exposure of the soil compartment is unlikely, and long-term tests may be required based on the outcome of a risk assessment.
- **Sediment toxicity:** Also long-term toxicity tests with sediment organisms may be needed if a risk to the sediment compartment has been identified.
- **Avian toxicity:** Long-term toxicity to birds is not needed if direct or⁸ indirect exposure of birds is unlikely.

⁵ Should probably read “and” in stead of “or”.

⁶ Should probably read “and” in stead of “or”.

⁷ Should probably read “and” in stead of “or”.

⁸ Should probably read “and” in stead of “or”.

4.4 Other Factors

For biocides and pesticides other factors may be decisive for whether data on a specific endpoint are needed. These are often related to either a specific use pattern of the substance or a specific mode of toxic action.

For biocides used as antifoulants, which are typically applied on ships and structures exposed to the marine environment, information on toxicity to aquatic plants and long-term toxicity to sediment organisms may be required if exposure and effect is likely. A study on bioconcentration in fish may be required as well, if the biocide has a potential for secondary poisoning. For insecticides, acaricides, etc., information on toxicity to honeybees is needed and for rodenticides, molluscicides, insecticides, acaricides, etc., information on acute and/or long-term toxicity to birds may be requested.

For pesticides used as insecticides, information on acute toxicity to an additional invertebrate species (e.g. insect) is required and for herbicides information on toxicity to an additional algal species and to an aquatic plant is required.

5. Conclusions

Based on the above review of testing or information strategies for various regulatory schemes, a number of conclusions on the current regulatory schemes can be derived:

- **New substances:** For notification of new substances, the information requirement is mainly driven by the quantity manufactured or imported, but also intrinsic properties and results of the risk assessment may influence the requirement.
- **Existing substances:** The review programme on existing substances in the EU is focussed on prioritised substances having a high potential for requiring risk management among those substances manufactured or imported in a quantity of > 1,000 tonnes per year per manufacturer or importer. For these substances, a minimum data set is obligatory, but based on the outcome of the risk assessment further data on fate and effects may be required for environmental compartments or types of organisms at risk.
- **Biocides:** Biocides are biologically active substances and, as such, the core data set comprises more data on intrinsic properties than are normally required for industrial chemicals. However, for environmental endpoints (in contrast to human health endpoints) the standard data set is limited, but further information may be needed or requested when exposure and thus potential risk is likely. To a large extent this depends on the intended use pattern of the biocidal product as designated by the product type.

- **Pesticides:** Also pesticides are biologically active substances and, as for biocides, an extensive core data set is normally required. The use pattern for pesticides is narrower than for biocides, but as pesticides are more often used on large areas, extensive data on fate and effects in the terrestrial environment are often needed.
- **Classification:** Classification is based on available information on intrinsic hazardous properties of chemicals and, as such, is not a driver for testing under the current EU legislation. However, an implicit testing strategy is built into some of the environmental criteria as additional data may be used for de-classifying a chemical that should otherwise be classified. In this context it is worthwhile noting that hazard classification is a main driver for other down-stream legislation concerning chemicals, i.e. regulations of chemicals at the workplace, use of chemicals in consumer products, transport of chemicals, waste containing chemicals etc.
- **PBT assessment:** The assessment of whether a substance fulfils the criteria for being a Persistent, Bioaccumulative and Toxic substance or a very Persistent and very Bioaccumulative substance follows a strategy where the use of animal tests as far as possible is avoided. Thus, the assessment begins with available screening data, but for the final assessment more specific tests may be needed starting with tests for persistence, eventually followed by tests for bioaccumulation and finally tests for toxicity.

The future information requirement for industrial chemicals according to the REACH proposal builds on the current requirements for new and existing substances, but is also inspired by the requirements for biocides and to a lesser extent pesticides. Thus, the information requirement under REACH is a more flexible system than under the current legislation, and it is built as an integration of the three main components from the current systems:

- **Volume:** As for new substances, the quantity manufactured or imported is the starting point for defining which data that are needed as the basis for assessing and documenting the safety of the substance. The system is, however, more lenient than the current system for new substances, as for most of the endpoints the tonnage trigger is a factor 10 higher under REACH than under NONS.
- **Hazard:** In contrast to the rather scarce specifications on information needs under current legislation on industrial chemicals depending on intrinsic (hazardous) properties, such information requirements have been extensively defined in the REACH proposal. The information referred to may relate to information from (Q)SARs, read across, grouping of chemicals, existing in vitro or in vivo data, including such data concerning other endpoints, if relevant for controlling the risk

from the endpoint in question. Examples of this more detailed information requirement under REACH are that, e.g., no testing of acute aquatic toxicity is needed for substances that are highly insoluble or are unlikely to cross biological membranes, no further degradation studies are necessary for substances that are documented readily biodegradable, and no sorption and bioconcentration studies are needed for substances which are not lipophilic. Such possibilities for waiving are also available today under the current legislation although sufficient justification is required.

- **Exposure or risk:** The information strategy in REACH takes over the approach from the existing substances review programme (and to some extent also the biocides legislation), where a likely exposure of and/or a potential risk to a certain environmental compartment trigger additional testing in order to better characterise the possible risk. This possibility for requiring or waiving a certain test can be used for most of the endpoints for which information is required for substances manufactured or imported in quantities above 100 tonnes per year and, for a few endpoints, even at a quantity of more than 1 tonne per year.

Thus, the information strategy described in the REACH proposal takes over and integrates approaches from the current legislation and merges them into a flexible information strategy. This flexibility may be explained by the fact that the regulation concerns both new and existing substances, and that account has been taken on use of already available information on existing chemicals concerning hazardous properties, risk and risk management. Furthermore, scientific progress has in general lead to increased possibilities for obtaining the necessary information without requiring new animal tests not only for existing substances but also for new. In reaching this conclusion, only the overall principles have been evaluated while no evaluation of data needs for various tonnages or the relevance of the properties triggering a test has been conducted.

Human Health

6. Introduction to Human Health Endpoints

In the REACH proposal for a new EU chemicals legislation, an ambitious goal has been set to gather information on 30 000 chemicals within the next 10 years. Due to economical and ethical reasons and the insufficient laboratory resources, the information requirements for most of the chemicals, i.e. those 20 000 chemicals manufactured or imported at 1-10 tons annually, are restricted to available information, *in vitro* data for skin irritation/corrosion, eye irritation and mutagenicity and data on sensitisation. Thus, appropriate and sufficient information for a complete hazard and risk assessment will only be available for a few endpoints.

The REACH proposal has also introduced the information strategy approach. It implies that before testing in accordance with the testing requirements in Annexes V-VIII, existing *in vivo*, *in vitro* and (Q)SAR data should be obtained, evaluated, and if data are appropriate and adequate, be used for hazard classification and chemical safety assessment. For some, but not all toxic endpoints, validated (Q)SAR models/approaches and *in vitro* tests should be used before proceeding to animal experiments. Exposure potential and risk management measures should also be considered, which may also reduce the need for animal testing.

In the REACH procedure, the testing and data requirements depend on the production volume: tiered test strategies are applied at various production volumes. Authorities are according to REACH obliged to judge whether new animal testing proposals put forward by industry are appropriate. On the other hand, although not obliged to, authorities may as part of the compliance consider check whether a proposal for waiving from animal testing is appropriate.

In this report we are comparing the information and testing requirements of the REACH proposal with the current information and testing requirements within the existing legislation for new and existing chemicals and the information strategy in the TGD. We also make comparison with the information requirements for classification according to the current EU classification criteria and the GHS criteria, which is expected to be implemented within the EU in the near future and thereby replace the current classification scheme.

7. Objective

For human health, the number of endpoints of concern is high. To restrict the task, we have in this scoping study report only considered a few endpoints, which may serve as examples for other human health endpoints. The selected endpoints are: acute toxicity, irritation/corrosion and reproductive toxicity.

8. Elements of the Information Strategies

The REACH proposal (COM 2003 0644 (03)), the revised TGD and the GHS as well as some of the recently approved OECD test guidelines have given some guidance on how to use the existing data, (Q)SAR, *in vitro* and *in vivo* tests. Furthermore, read-across, i.e. evaluation based on studies with structurally similar compounds has been included in some information strategies. The REACH proposal has also introduced exposure driven testing to a certain degree. These elements need to be considered in the information strategy and the relevant guidance given by EU for information strategies should assist the use of these elements.

8.1 *Use of Existing Data*

For many industrial chemicals produced in large volumes, a number of articles and reports can be found in the open literature. The studies are not always made according to GLP and standardised testing methods (OECD/EU test guidelines). A GLP study gives reassurance of the availability of original data, identifies responsible persons and enhances the acceptance of the study internationally. In case of a non-GLP study, published or unpublished, the documentation should be transparent enough to enable an assessment of the study quality. However, a study performed according to standardised OECD testing methods, does not by itself guarantee that it is the most appropriate study protocol. A study with a more specific test protocol designed to answer a certain question, which does not follow a standardised OECD protocol may even be of higher value than a study following the guidelines. For example, it may give supportive evidence of the mechanism of a substance to induce a harmful effect. Concerning human data, valid epidemiological studies are often important for the assessment of long-term effects, e.g. carcinogenicity. Case reports could also be of value in the assessment of health hazards, e.g. on acute toxicity and sensitisation.

Sources of unpublished data are numerous, including e.g. the screening test data of industry and observations of occupational health personnel of industry and poison information centres.

The use of existing data is acknowledged by the EU TGD and the OECD Guidance Document, which both describe how to use such data. It is worthwhile to consider, whether and how these data could be increasingly used in chemicals control in relation to classification and risk assessment.

It should be noted, that for new substances placed on the market, neither animal test data nor human data are available in the open literature. However, other relevant information may be available such as (Q)SAR.

8.2 (Q)SAR

The use and reliability of (Q)SAR models/approaches for the selected endpoints will be further analysed in part 2 of this project.

8.3 Read Across

Read across, i.e. the consideration of structural similarity in evaluation of the toxicity of chemicals is a potential element of information strategies. It is based on the assumption that the reactive groups of chemicals molecular structure determine its toxic properties. Of course these are modified by molecular weight and other factors, which e.g. affect the permeability characteristics. Structural similarity or structural relations are a part of many information strategies summarized in tables 1-3 below. The use of read across will be further analysed in step 2 of this project.

8.4 In Vitro Tests

In vitro methods are considered to be non-animal tests even though some of the tests include use of e.g. organs, tissues or sub-cellular fractions from animals. In vitro methods are an area with high focus and under continuous development, mainly due to the political pressure to meet the animal welfare goals (i.e. to reduce the number of animals used for chemicals testing as much as possible and to minimise animal suffering). In addition, in vitro methods have other advantages, such as being inexpensive, quick, relatively easy, of short duration and rather efficient testing systems.

In vitro tests have been used for regulatory purposes for many years. In general, in vitro tests provide supplementary information, which may be used in relation to the interpretation of the relevance for humans of data from animal studies or to get a better understanding of the toxicological mechanism of action of the substance. Furthermore, in vitro methods may be used as screening tests for priority of animal confirmatory tests. In that respect a good screening test is a test with high sensitivity.

ty⁹ and a reasonable specificity implying that the test may have a few false negative and a reasonable low level of false positives. In some few cases *in vitro* methods may be used to replace the animal testing currently required for hazard and risk assessment. In that respect most progress has occurred in the areas of local (ocular and dermal) toxicity, target organ toxicity and mutagenicity, whilst there has been little progress in the use of *in vitro* tests for predicting overall systemic toxicity.

8.5 In Vivo Tests

In vivo data for regulatory purposes may include human data (e.g. epidemiological data and case reports) and experimental animal data preferably performed according to international accepted guidelines (OECD test guidelines or 67/548, Annex V methods). Animal experiments and good quality positive human data are usually considered as sufficient data for classification and risk assessment. However, according to the existing approach (Annex VI) negative human data should not overrule positive animal studies, whereas in special cases hazardous properties detected in animal experiments may be disregarded if it can be justified that the findings in animals are not relevant for humans.

Test results from mammalian laboratory animal studies are particularly useful for human health hazard classification and risk assessment. Such studies consider various toxicological endpoints of concern, e.g. acute toxicity, irritation/corrosion, sensitisation, repeated dose toxicity, carcinogenicity, mutagenicity and reproductive toxicity. In addition, in certain cases information on toxicological mechanism may be needed, as it may be necessary to get some basic understanding of the mechanism to be able to decide on an appropriate testing strategy for the substance.

In relation to the continuous revision of Test Guidelines there has been a tendency to decrease the number of animals used and to develop screening studies. Whereas the animal welfare goal is supported, it should, however, be noted that the use of screening studies may reduce the robustness of the hazard assessment.

8.6 Exposure Driven Testing

In the REACH proposal and the TGD, potential exposure is considered in information strategies of some endpoints at higher tonnages. Main considerations should include consideration on the use of the substance also in preparations and the use of the preparations, exposed populations (i.e. workers, consumers and/or the general population (food and drinking water) including susceptible groups, and relevant routes of exposure).

⁹ Sensitivity: Fraction of positives (percentage of correctly identified “positives” when “positives” are identified as chemicals having an undesirable effect e.g. mutagenic or sensitising).

Specificity: Fraction of negatives (percentage of correctly identified “negatives” of the true negatives).

Chemicals should be tested using those routes of exposure (skin, oral, inhalation), which are relevant in terms of the known exposure scenarios for the substance and preparations/products containing the substance. For example substances with very low vapour pressure should only be tested for inhalation toxicity if inhalation exposure to aerosols or dust containing the substance is considered relevant.

Another example is that within the reproduction toxicity information requirement of REACH, in vivo tests are not needed if humans are not exposed to the substance, and according to the TGD, requirements can be modified, depending on the anticipated use and the human exposure pattern. In the Annex VI (Directive 67/548/EEC) exposure is not used as a criterion. Guidance on how to obtain the exposure data and how it can be used to avoid unnecessary testing is not given in the REACH.

Tonnage-based Information Strategies

Overview of the tonnage based information/test requirements of various legislations is given in the Annex 1, below. The table covers tonnage levels indicated in:

- REACH,
- Regulation on existing substances (Annex III of 793/93),
- Directive on Notification of New Substances (Annex VII 92/32/EEC) and
- Guidance given of the HPV program of the OECD.

The tonnage-based requirements in REACH are different compared with the three other information strategies (summarized in the Appendix B of this report). This is understandable since the focus in the Existing Substances Regulation and OECD HPV Program is on high production volume chemicals and the only level that has been set is 1000 t/a. The outline of these two information strategies is rather similar. The tonnage levels for information requirements set for new chemicals in the EU are very low as compared with the other three. In REACH, the distinctions between “existing” and “new” chemicals will be replaced by the terms phase-in and non phase-in substances, respectively. The 1000 t/a phase-in substances need to be registered within 3 years, whereas non-phase-in substances will be registered immediately.

Note that the Annex III of 793/93 only gives a list of information requirements, whereas in the TGD, for example existing data, exposure, (Q)SAR and in vitro data are often considered together with specific tests. Thus, Annex III is a list of information requirements, whereas TGD gives a detailed information strategy. In the Annexes of the REACH proposal, specific rules have been given for adaptation of information requirements; these rules are not indicated in detail in the Appendix B of this report, however, some examples are given in the footnotes. Rules of

adaptation, which are an important part of the information strategy of REACH, are included in the respective tables 1-3 below.

More details on how potential exposure is considered in information strategies are given in tables 1-3.

9. Inventory and Comparison of Existing Information Strategies and Criteria for Classification

In the chapters below, a comparison between the information strategies of the REACH proposal and the TGD are made, as well as with the classification criteria of the Annex VI (Directive 67/548/EEC) and GHS¹⁰. This comparison is considered relevant because information strategies given in any part of the legislation should provide data, which are adequate for classification, risk and PBT assessment and any decisions concerning risk management.

9.1 Acute Toxicity

Acute oral or dermal toxicity refers to those adverse effects occurring following oral administration or dermal application of a single dose of a substance, or multiple (oral) doses given within a short time (24 hours, oral exposure, rat). Acute inhalation toxicity refers to adverse effects occurring after a single uninterrupted exposure by inhalation of an inhalable substance over a short period of time (24 hours or less, rat). Acute toxicity excludes local irritation or corrosive effects. Endpoints of concern are according to GHS, existing OECD Test Guidelines and the current EU classification criteria e.g. death (according to older test methods), evident toxicity, irreversible damage, target organ systemic toxicity/single exposure, aspiration hazards and narcotic effects.

REACH Proposal

In the REACH proposal, information on acute toxicity is not required at tonnage levels below 10 tonnes. At the tonnage level of 10-100 t/a and above, data on oral acute toxicity should be provided, unless the substance is a gas or volatile liquid. In that case acute toxicity information should be provided for the inhalation route. In the strategy, existing data (e.g. from clinical reports, poisoning cases, animal studies, or on corrosivity, physical-chemical properties), should be considered (see table 1). Other elements of the information strategy, e.g. in vitro studies, systemic effects observed in other studies, route of human exposure, physical-chemical properties, dermal or respiratory toxicity of structurally-

¹⁰ The criteria for classification in Annex VI and in GHS do not include testing schemes, and authorities cannot require tests solely by reference to lack of or insufficient data.

related substances, are primarily used in the selection of either acute in vivo inhalation test or acute in vivo dermal test. No specific reference is made to validated (Q)SAR models/approaches or to validated in vitro methods, but such data should be assessed when available. Acute toxicity testing of corrosive substances should be avoided at levels that are corrosive according to the test guidelines and should therefore be performed at non-corrosive levels. However, according to the REACH proposal, acute toxicity studies should not be conducted if a substance is corrosive. There is no reference to classification criteria, i.e. it is not clear whether this is only valid for substances that are classified for skin corrosion and thereby subject to risk management measures.

TGD

In the TGD for acute toxicity, a detailed information strategy is given for new substances, which also could be followed for prioritised existing substances when data are lacking and new tests have to be performed. Normally, acute oral toxicity test is initially performed. Consideration should be given as to whether the substance is corrosive. For the choice of a second route of administration, if motivated, observations on systemic toxicity from the oral route and other studies should be considered. The inhalation route should be chosen for gases/aerosols and dermal route if e.g. there is a potential for high dermal exposure. In the strategy, existing data (especially from skin/eye irritation, skin absorption and skin sensitisation studies), data on physical-chemical properties, corrosion, potential exposure, and in vivo tests are utilised (see table 1). However, these data are primarily used for consideration of the need for testing either for acute inhalation toxicity or acute dermal toxicity. No specific reference is made to validated QSAR models/approaches and no validated in vitro method is recognised. However, it is stated that methods using “structural alerts” may provide useful information for assessment of the acute toxicity of certain substances (e.g. for highly water soluble salts of substances with well characterised toxic properties, the systemic toxicity can be expected to be similar).

If a substance is predicted to be corrosive, an acute oral study may not be justified. However, in figure 5 in the TGD, an acute inhalation test should be considered for corrosive gases but at non-corrosive concentrations. For acute dermal toxicity, there is a choice in fig. 5 of the TGD to either classify (in which category is not discussed) or perform the test at non-corrosive levels.

For existing substances, the minimum requirements for priority list substances are identical to those for new substances at base set (1 tpa). The information strategy for existing substances is not as detailed as that for new substances. Evaluation of existing data, potential for human exposure and in vivo tests are the elements considered for the existing substances.

Annex VI (Dir 67/548/EEC)

Classification of substances for acute toxicity is based on tests in animals and/or on existing human data (e.g. from poisoning cases). Classification of aliphatic, aromatic or alicyclic hydrocarbons for aspiration hazard is based on human data or physico-chemical properties such as viscosity and surface tension. Furthermore, classification for narcotic effects is based on volatility and results from in vivo animal studies or practical experience in humans. Otherwise, physico-chemical data, exposure potential for humans and in vitro tests are not considered. Obviously, the data requirements of REACH imply that chemicals produced or imported at 1-10 t/a cannot always be classified for acute toxicity because REACH does not require information on acute toxicity for this tonnage band.

GHS

Similarly as with the Annex VI criteria, the assessment of whether the GHS criteria are fulfilled should in general be based on in vivo animal experiments, where oral, inhalation and dermal routes of administration are applied. Moreover, in GHS, Classification in category 5 (i.e. LD50/LC50 is 2000-5000 mg/kg bodyweight) for general acute toxicity is based on in vivo tests, reliable information on toxicity in humans, mortality at lower dose levels, expert judgements of clinical signs observed in the in vivo test, or expert judgement of effects seen in other animal studies. However, testing in animals in Category 5 range is discouraged.

Summary

Both the two testing schemes as well as the criteria for hazard classification rely on or require primarily in vivo data and/or evidence from human poisoning cases. According to the REACH proposal and the TGD, physico-chemical properties, potential exposure and data on in vitro percutaneous absorption can be utilised, when the exposure route or the need altogether for a further in vivo study is considered. The in vitro test battery, refined in the EU research EDIT project, may depending on its validation be a useful element for the acute toxicity information strategy. Similarly, (Q)SARs may if successfully validated also in future be used in an acute toxicity information strategy. However, increased use of in vitro data as well as (Q)SAR model predictions for evaluation of acute mammalian toxicity in an integrated information strategy has to be linked not only to the scientific validation of such information, but also to the regulatory acceptance, i.e. in relation to the usefulness for hazard classification, (initial) risk assessment and PBT assessment.

Table 1. Summary of acute toxicity information strategies and data requirements in the REACH proposal and Technical Guidance Document (TGD) in comparison with classification criteria in Annex VI, Dir 67/548/EEC and in the Globally Harmonised System (GHS)

ACUTE TOXICITY	Information requirements and testing strategies		Classification criteria	
	REACH proposal	TGD, EU Guidance on Risk Assessment	Annex VI	GHS
Use of existing human, animal and other data	Information on acute toxicity not required below 10 tpa. Above 10 tpa, the registrant shall as a first step compare the information needs for the substance with the existing data and identify data gaps	Existing information from a wide range of tests and reports can be used to determine the acute toxicity.	Classification is based on human or animal data. For aspiration hazards, classification is based on human data or viscosity and surface tension. For narcotic effects, volatility and results of in vivo animal studies or practical experience in humans are used for classification.	Classification is based on human or animal data.
Physical and chemical properties	Vapour pressure, particle size and aerosol formation as well as dermal absorption, lipid solubility and molecular weight are considered when dermal or inhalation acute toxicity test is selected.	Are mentioned in the information strategy for new substances, for consideration of the need to test for acute dermal toxicity (e.g. low log K_{ow} refers to low dermal absorption).	Not considered specifically for general acute toxicity. For labeling (but not for classification) there is a general possibility not to label massive metals, alloys, polymers etc (para. 8.3 and 9.3) if they do not present a danger to human health, or environment. For aspiration, classification could be solely based on viscosity.	Not considered specifically for general acute toxicity.
(Q)SAR and read across	Not considered specifically for acute toxicity. However, if structurally similar compounds are acutely toxic via dermal route or easily absorbed, in vivo dermal toxicity test may be appropriate.	"There are currently no validated in vitro methods for acute tox. But methods using "structural alerts" may provide useful information for assessment of the acute toxicity of certain substances (e.g. for highly water soluble salts of substances with well characterised toxic properties, the systemic toxicity can be expected to be	Not considered specifically for acute toxicity (only mentioned in general terms for all endpoints in para. 1.6.1. "the results of validated structure-activity relationships and expert judgement may also be taken into account where appropriate"). Aliphatic, alicyclic and aromatic hydrocarbons could be classified for aspiration hazard.	Not considered

		similar)". SAR is mentioned in the information strategy for new substances for consideration of corrosive potential to be considered if testing for acute tox.		
Potential Exposure	Route of human exposure is considered when the second administration route in the in vivo testing is selected. (For substances other than gases and volatile liquids, the oral route should always be tested). E.g. if skin contact is likely in production and/or use, <i>in vivo</i> dermal toxicity testing should be considered.	Testing for dermal toxicity is indicated e.g. when there is a potential for high dermal exposure. (For substances other than gases and volatile liquids, the oral route should always be initially tested).	Not relevant.	Not relevant.
In vitro tests	In vitro dermal absorption data is considered when available.	There are currently no validated in vitro methods for acute toxicity. However, in the information strategy for new substances the potential for corrosivity should be considered before testing for acute tox.	Not considered.	Not considered.
In vivo tests	Information on acute toxicity not required below 10 tpa. If the substance is corrosive or flammable an in vivo study need not be conducted Oral and dermal/inhalation acute toxicity data are needed for substances produced or imported >10 tonnes/a. Criteria are outlined for when a dermal and an inhalation test should be performed (see above)	Available methods are: Fixed dose procedure, toxic class method, up-and-down method, LC ₅₀ , dermal LD ₅₀ . Note: Oral LD ₅₀ has been deleted from annex V. At least two routes of exposure should be tested.	Classification is based on LD ₅₀ , LC ₅₀ , acute toxic class method, or fixed dose method. In these tests, irreversible damage, and e.g. narcotic effects could be observed.	Classification is based on LD ₅₀ , LC ₅₀ , acute toxic class method, fixed dose method. In these tests symptoms of target organ systemic toxicity, such as narcotic effects could be observed

9.2 Irritation / Corrosion

Irritation and corrosion are considered as local effects. According to the criteria in Annex VI (Directive 67/548/EEC) a corrosive substance produces full thickness destruction of skin tissue and the damage is irreversible. Skin irritating substances cause significant inflammation of the skin. The findings are usually reversible erythema, eschar formation or oedema. Eye irritants cause significant ocular lesions with corneal opacity, iritis or conjunctival redness. Some substances may cause severe ocular lesions and thus cause serious damage to the eyes. This is the case also if a substance causes colouration of the eyes. Local respiratory irritation is usually limited to the upper airways and is reversible.

REACH Proposal

Available human and animal data, physico-chemical properties, *in vitro* data (from 1-10 t/a level) and *in vivo* data (from 10 t/a level) are the elements of the REACH information strategy (see table 2). The *in vivo* and *in vitro* tests for skin irritation and corrosion are not necessary if the substance is corrosive, strongly acidic or basic, flammable at room temperature, dermally very toxic or not irritant in a limit test (up to 2000 mg/kg b.w.). The *in vivo* test is also not necessary if classification can be based on data obtained, when the information strategy at 1-10 t/a level is completed. Additionally, for eye irritation *in vitro* or *in vivo* tests are not necessary if the substance is classified as irritant in contact with skin and the registrant classifies the substance as an eye irritant. The *in vivo* test is also not necessary if classification can be based on data obtained, when the information strategy at 1-10 t/a level is completed. Respiratory irritation is not mentioned in the REACH as such, but the requirement to provide any other relevant information should cover this if the information is available. Alternative data e.g. from (Q)SARs and read-across from other substances must be collected in the registration phase.

The information strategy of the REACH proposal is very similar to the testing strategies given in the Annexes of OECD test guidelines 404 and 405 as well as in the irritation/corrosion criteria of the GHS. However, in REACH, waiving from testing for corrosion/irritation is possible if the substance is flammable in air at room temperature, but this is not mentioned in the OECD TG, which is a discrepancy. In the REACH proposal, exposure is not considered in the specific rules for adaptation as a waiving tool for corrosion and irritation.

There are two *in vitro* test methods available in the OECD Guidelines, which allow the identification of corrosive chemical substances and mixtures. For identification of non-corrosive substances and mixtures negative *in vitro* test data have to be supported by a weight of evidence determination using other existing information, according to the guidelines. For eye irritation, there are no validated and formally approved *in vitro* tests. An EU declaration was proposed in 2002 for the acceptance of posi-

tive *in vitro* data on severe eye irritation; however, the present status of the declaration is unclear. Validated and formally approved *in vitro* tests for skin irritation are not available. Consequently, not all provisions of REACH at the 1-10 t/a level can be implemented at the moment.

TGD

Existing human and animal data, physico-chemical properties, *in vitro* and *in vivo* data are the elements of the TGD information strategy (see table 2). The testing strategy in the TGD emphasises the need to evaluate all available information before attempting any *in vivo* testing. For skin and eye irritation, but not for respiratory irritation, there are *in vivo* test methods in Annex V to Directive 67/548/EEC. When evaluating animal studies non-guideline tests may be taken into consideration if the test results are consistent. Attention should be given to persisting irritating effects even if they don't lead to classification. Data from general toxicity studies may provide useful information on local effects on skin, eyes and mucous membranes and respiratory tract. Generally, in human risk assessment the use of SARs may be considered when data do not exist for a given endpoint or when data are limited; however, it is recognised that SAR techniques and methods are not well developed in relation to mammalian toxicology. If *in vitro* tests for irritation give clear indications of irritative properties this may be sufficient for hazard identification purposes. However, data from *in vitro* studies alone would not be considered sufficient to define a substance as being non-irritating. The TGD also mentions that physico-chemical data can be used to identify a substance as being corrosive, but not as being non-irritant. Physico-chemical properties or practical experience may also indicate that a substance has defatting properties, which may cause irritation. The information requirements for irritation and corrosion are essentially the same for new and existing substances. Exposure is not considered in the effect assessment.

The information strategy of the TGD is rather similar to the ones given in the Annexes of OECD test guidelines 404 and 405 as well as in the criteria for classification in the GHS.

Annex VI (Directive 67/548/EEC)

Available human and animal data, physico-chemical properties, known properties of the chemical group (organic hydroperoxides) and *in vitro* and *in vivo* test data are the data elements of the Annex VI (see table 2).

Classification for skin corrosivity can be based on the results of validated *in vitro* tests, such as those cited in Annex V to Directive 67/548/EEC. Strong acids and strong bases can be classified for corrosivity, i.e. when pH is equal or less than 2.0 or when pH is equal or more than 11.5. In these cases the acid/alkali reserve may also be taken into consideration. Organic hydroperoxides are usually classified as corrosive.

Criteria for classification for skin irritation include *in vivo* test data. Human data and non-acute animal studies can also be used. Organic peroxides are usually classified as corrosive or irritating unless when there is evidence to the contrary. Classification for eye irritation is based on *in vivo* studies and practical experience in humans. An EU declaration was proposed in 2002 for the acceptance of positive *in vitro* data on severe eye irritation; however, the present status of the declaration is unclear. (Q)SAR models/approaches have been of limited use in the classification scheme for irritation/corrosion (there is no specific reference to (Q)SAR data in the specific classification criteria for irritation/corrosion). Exposure is not considered in classification.

Classification for respiratory irritation shall be based on practical observations in humans and positive results from appropriate animal tests. The latter refers e.g. to data obtained in a general toxicity test including histopathological data from the respiratory system.

It can be concluded that classification for skin irritancy of substances in the REACH proposal at the 1-10 t/a level can remain open if available data do not indicate that the substance is irritating, since an *in vitro* test for skin irritation is not yet available. The same applies for eye irritation if the non-validated *in vitro* tests are not accepted and a substance is not already classified as a skin irritant. Non-corrosivity may also be left open at the 1-10 t/a level if negative *in vitro* data are the only data available on corrosivity.

GHS

Existing human and animal data, information from structurally similar compounds and on extreme pH values as well as validated and accepted *in vitro* test data can be used when the corrosion and irritation potential are determined for skin and eyes. It is emphasised that all relevant information that is available on a chemical should be used when determining the need for *in vivo* testing of skin irritation/corrosion and eye irritation. Validated and accepted SAR/SPR approaches are specifically mentioned in the testing strategy for eye irritation. Similarly to the REACH proposal, GHS indicates that it may not be practicable to conduct skin irritation/corrosion studies, if a chemical is dermally highly toxic. Moreover, possible skin corrosion has to be evaluated before testing for serious eye damage/eye irritation is considered. Scheme of tiered testing and evaluation, similar to those in the Annexes of the OECD test guidelines 404 and 405, are given in the GHS. Exposure potential is not considered.

Respiratory irritation will be covered by GHS later on.

Compared to the Annex VI criteria, read-across and expert judgement is more prominently considered in the GHS.

Summary and Remarks

In each of the two testing schemes (REACH and TGD) and the two systems of criteria for classification (Annex VI and GHS), existing human and animal data, physico-chemical data, structure-activity relationships and *in vitro* and *in vivo* test data are considered. Generally, all existing data should be considered, and as the very last resort *in vivo* testing should be conducted.

Classification for corrosivity can be based on *in vitro* data; however, the OECD Guidelines 430 and 431 for *in vitro* corrosivity state that negative results need confirmation by other supportive data. For skin and eye irritation there are no *in vitro* test guidelines or (Q)SARs, available, which have been validated and formally accepted by regulators for classification and/or risk assessment. For the REACH testing approach it means that skin and eye irritation cannot always be evaluated at the 1-10 t/a level. The absence of corrosive properties at that tonnage level can also not be established in all cases.

Respiratory irritation is not mentioned as such in the REACH proposal, but there might be relevant information available. The guidance that will be prepared for the REACH information strategies should cover respiratory irritation as well.

It should be considered, whether certain groups of chemicals, such as strong oxidants or acids/bases, could be considered irritating/corrosive without testing in REACH.

Table 2. Skin and eye irritation/corrosion information strategies and data requirements in the REACH proposal and the Technical Guidance Document and the classification criteria (Annex VI of Directive 67/548/EEC and GHS)

SKIN AND EYE IRRITATION/CORROSION	Information requirements for risk assessment		Classification criteria	
	REACH proposal	TGD	Annex VI	GHS
Use of existing human, animal and other data	Available human and animal data is evaluated. Eye irritation test is not needed, when a substance is classified as a skin irritant. Skin irritation/corrosion tests are not needed if the substance is very toxic to skin or if an acute toxicity study by dermal route does not indicate skin irritation up to the limit dose level (2000 mg/kg body weight).	All available data should be evaluated before <i>in vivo</i> testing; reference is made to the information strategies attached to B.4 and B.5 in Annex V of 67/548.	Available human and animal data should be evaluated, as well as pH and data from validated <i>in vitro</i> tests.	Existing observations and data from humans and animals should be analysed. If a chemical is highly toxic by dermal route, a skin irritation/corrosion study may not be practicable. Outcome of skin irritation testing should be taken into account when determining the need for <i>in vivo</i> eye irritation testing.
Physical and chemical properties	<i>In vitro</i> and <i>in vivo</i> tests are not needed, if the substance is corrosive or a strong	Data on physical and chemical properties can be used to identify a substance	Substance is considered corrosive if pH is ≤ 2 or \geq	Substance is considered corrosive if pH is ≤ 2 or ≥ 11.5 (especially when buffering

	acid (pH<2.0) or a strong base (pH>11.5), or flammable.	as being corrosive, but not as being non-irritant.	11.5. Where classification is based upon consideration of extreme pH alone, R35 (Causes severe burns) should be applied.	capacity is known).
(Q)SAR and read across	Needs to be considered.	Needs to be considered when other data are limited.	Are considered on a case-by-case basis. Organic hydroperoxides are classified with R34 (Causes burns) or R38 (Irritating to skin) or R36 (Irritating to eyes)	Structure activity relationship or structure property relationship are considered.
Potential Exposure	Not considered.	Not considered.	Not considered.	Not considered.
In vitro tests	<i>In vitro</i> skin irritation, skin corrosion and eye irritation tests are requested as a last resort for chemicals produced or imported 1 tonne/a or more. Note exemptions.	<i>In vitro/ex vivo</i> tests should be made before animal testing. Clear indications that a substance is likely to be irritant may be sufficient for hazard identification purposes. Data from <i>in vitro</i> studies alone would not be considered sufficient to define a substance as being non-irritating.	Classification for corrosivity can be based on the validated <i>in vitro</i> tests in Annex V, B.40. It is mentioned that in general where there are validated <i>in vitro</i> test methods in Annex V, these tests should be used where appropriate.	Validated and accepted <i>in vitro</i> tests may be used for classification. However, it is recognised that there are no validated <i>in vitro</i> test methods for skin irritation, but for skin corrosion.
In vivo tests	<i>In vivo</i> skin and eye irritation tests may be needed for substances produced or imported 10 tonnes/a or more. Note exemptions.	New substances: in general, only tests using Annex V methods are adequate. Existing substances: the basic requirements are identical to those for new substances but there is more flexibility as to how data are obtained and <i>in vivo</i> tests should be considered as a last resort.	Corrosion may be determined by <i>in vivo</i> test of Annex V. Irritation to skin and eye are determined by <i>in vivo</i> tests of Annex V.	All relevant information that is available on a chemical should be used in determining the need for <i>in vivo</i> skin irritating/corrosion testing and eye irritation testing. Animal testing with corrosive substances should be avoided whenever possible.

9.3 Toxicity to Reproduction and Development

Reproductive toxicity includes impairment of female and male reproductive functions or capacity and the induction of non-heritable harmful effects on the progeny. Effects on male and female fertility includes adverse effects on libido, sexual behaviour, any aspects of spermatogenesis or oogenesis, or on hormonal activity or physiological response which would interfere with capacity to fertilise, fertilisation itself or the development of the ovum up to and including implantation. Developmental

toxicity is taken in its widest sense to include any effects interfering with normal development, both before and after birth. It includes effects induced or manifested prenatally as well as those manifested postnatally. This includes embryotoxic/fetotoxic effects such as reduced body weight, growth and developmental retardation, organ toxicity, death, abortion, structural defects (teratogenic effects), functional defects, peri-postnatal effects, and impaired postnatal mental or physical development up to and including normal pubertal development.

REACH Proposal

In the REACH proposal, information on reproductive toxicity is not required at tonnage levels below 10 t/a. Available human and animal data, (Q)SAR models/approaches, potential exposure, known properties of the chemical group, in vitro data and in vivo data (above 10 t/a level) are the elements of the REACH information strategy (see table 3).

At 10-100 t/a level, *in vivo* screening for reproductive/developmental toxicity (TG 421) and developmental toxicity study (TG 414) are requested. The studies do not need to be conducted if the substance is known to be a genotoxic carcinogen or germ cell mutagen and appropriate risk management measures are implemented or relevant human exposure can be excluded. (See table 3). The *in vivo* screening study is required 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. A positive result in the screening study shall be confirmed at this level by a developmental toxicity study (i.e. TG 414). The developmental toxicity study (TG 414), however, seems to be requested also in the absence of positive results in the *in vivo* screening for reproductive/developmental toxicity (TG 421) as both studies are included under the heading "Standard information required". The study shall be initially performed on one species and a decision on the need to perform a study on a second species should be based on the outcome of the first test.

Above 100 t/a, developmental toxicity study (TG 414) and two-generation reproductive toxicity study (TG 416) are required, except for genotoxic carcinogens and germ cell mutagens, where appropriate risk management measures are implemented. The two-generation study is at this level only required, if the 28- or 90-days study indicates adverse effects on reproductive organs or tissues.

Above 1000 t/a, the two-generation reproductive toxicity study is required, except for genotoxic carcinogens and germ cell mutagens, where appropriate risk management measures are implemented. Also, the study need not to be conducted if the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven that no systemic absorption occurs via relevant routes of exposure, and there is no or no significant human exposure.

Generally, the two-generation study is required in one animal species. The developmental toxicity study shall initially be performed on one species and a decision on the need to perform a study on a second species should be based on the outcome of the first test.

TGD

The TGD states under the heading “Minimal data requirements” that “In order to fully assess the hazardous properties of a substance with respect to reproductive toxicity, the key data requirements for new substances, existing substances and biocides are: A two-generation study (OECD TG 416 or corresponding Annex V method), **and** a prenatal developmental toxicity (teratogenicity) study in two species (OECD TG 414 or corresponding Annex V method).” In addition, it is stated that the need for inclusion of developmental neurotoxicity evaluation must be considered.

It is, however, also stated that these key requirements can be modified, either as reduced testing or as a need for accelerated or extended testing, depending on the regulatory program, and influenced by available evidence.

The TGD gives detailed guidance on a stepwise approach with regard to reproductive toxicity for new substances (see table 3). In relation to the sequence of testing, the first specific reproductive toxicity test should usually be the two-generation test. For existing substances, the testing sequence outlined for new chemicals should be followed and derogations from the minimum data set (i.e. OECD TG 414 in two species and OECD TG 416 in one species) may be agreed on a case-by-case basis following the same principles as described for new substances. In summary, the TGD identifies similar minimum data requirements and recommends similar testing strategies for new and existing chemicals, but recognizes that the possibility for derogations based on available evidence may differ among new and existing chemicals.

Available human and animal data, (Q)SAR models/approaches, potential exposure, known properties of the chemical group, in vitro data and in vivo data (above 10 t/a level) are the elements of the TGD information strategy (see table 3). For germ cell mutagens and genotoxic carcinogens that respectively meet the criteria for classification as Category 1 or 2 mutagens and Category 1 or 2 carcinogens, reproductive toxicity testing will normally not be required, unless there are case-specific reasons to indicate that the information gained from testing will be needed for the risk characterisation. Well-reported epidemiological studies and relevant animal studies (e.g. 90 day study) are considered when testing requirements are set. Furthermore, data requirements and testing programme may be modified depending on SAR, potential exposure and structural relationships with a known reproductive toxicant.

Testing is generally not required below 10 t/a, but may be required under specific circumstances, i.e. when there is a particularly high con-

cern for reproductive toxicity, based on other toxicity studies and/or SAR consideration and when it is expected that reproductive toxicity may occur at doses close to known or estimated human exposure levels. The first test to be conducted, and the timing of subsequent reproductive toxicity test, should be decided on a case-by-case basis, taking into account the nature of the anticipated effect and the exposed population.

At the tonnage level of 10-100 t/a, the two-generation study should be performed when there are indications of potential reproductive toxicity or widespread human exposure predicted difficult to control. The first specific reproductive toxicity test to be conducted should usually be the two-generation study. The developmental toxicity study is recommended performed when there are serious concerns from SAR and potential human exposure, or indications of likely developmental toxicity from the two-generation study.

Above 100 t/a, a two-generation study and a prenatal developmental toxicity study is recommended. If there is low biological activity and no evidence of significant absorption and low concern in relation to exposure, it may be considered to delay the reproductive toxicity testing to the tonnage level of 1000 t/a.

The *in vivo* screening reproductive /developmental toxicity tests OECD 421 and 422 are not part of the testing strategy in the TGD, but the TGD states that clear “positive” results may identify a substance as toxicity to reproduction, while the methods will not provide evidence for definitive claims of no effect.

Generally, the TGD states that the need for inclusion of a developmental neurotoxicity evaluation must be considered at the planning stage of the two-generation study and the developmental toxicity study. The OECD draft TG 426 developmental neurotoxicity study is mentioned and guidance is given on e.g. triggers for testing, evaluation of the results and the need for further actions.

Annex VI (Directive 67/548/EEC)

Specific epidemiological data, potential exposure, relationship to a known anti-fertility agent, *in vitro* and *in vivo* data are the elements of the Annex VI (see table 3). (Q)SAR approaches are not considered in the specific criteria and the role of *in vitro* studies is minor. In general, only clear epidemiological evidence or evidence from relevant animals studies, sometimes supported by other data (see table 3) leads to classification for reproductive toxicity. For classification in category 2 and 3, however, “Other relevant information” may be a basis for classification. This has generally been used and was most probably meant to indicate that “other relevant information” may influence the decision on classification based on the results of animal studies.

In vitro studies are regarded as “supportive evidence” only. A strict view to the available data has been chosen in the Annex VI: only “suffi-

cient epidemiological evidence on causal relationship” is regarded useful, in that case a substance is classified with Repro Cat. 1.

GHS

The classification criteria of GHS include evidence from humans (ideally from well conducted epidemiological studies, category 1A), and clear evidence from animal studies (category 1B). When there is evidence, which is not strong enough to place a substance to category 1, then category 2 may be selected. In that case, the effect to reproduction may also “be a secondary non-specific consequence of other toxic effects.” Other data from sub-chronic and chronic animal studies, which provide information regarding toxicity on reproductive and endocrine organs, may be considered when the “the total weight of evidence” is assessed. “Evaluation of substances chemically related” may also be included. Toxicokinetic studies in animals and humans may provide information, which could reduce or increase concerns about the hazard. Evidence from *in vitro* assays and from SAR can contribute to classification. There is a general agreement on the concept of a limit dose above which adverse effects may be considered outside the criteria leading to classification. However, there was no agreement of a specified dose as a limit dose.

Discussion and Conclusion

In the two testing schemes (REACH and TGD) and in the two sets of criteria for classification (Annex VI and GHS), existing human and animal data, potential exposure, structural similarity to known reprotoxicants as well as *in vitro* and *in vivo* data are considered.

There are some potentially important differences between the information requirements/testing strategies in the REACH proposal and the TGD. These include:

- 1) The use of data from structural relationship, (Q)SAR
- 2) The role of the screening test for reproductive/developmental toxicity (OECD 421)
- 3) The use of potential human exposure
- 4) The sequence of testing using two-generation study and developmental toxicity study
- 5) The need for developmental neurotoxicity data
- 6) The use of the one-generation study

Ad 1) In the REACH proposal, it is stated at tonnage level >10 t/a that the screening test for reproductive/developmental toxicity (OECD 421) is required 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”. This seems to imply that the screening test is not required if there is evidence from available

on structurally related substances, from (Q)SAR estimates or from in vitro methods that the substance may be a developmental toxicant. Consequently, within the REACH, it seems that positive evidence from available data on structurally related substances, from (Q)SAR estimates or from in vitro methods that the substance may be a developmental toxicant is considered as sufficient at the 10-100 t/a level for registration and risk assessment. In the TGD, however, such evidence can only be used for deciding that reproductive toxicity testing should be performed at >10 t/a instead of 100 t/a.

In terms of the practical implementation of the REACH proposal, it is noteworthy that validated (Q)SAR models/approaches or validated in vitro methods for reproductive toxicity are not available at present.

Ad 2) The screening test for reproductive/developmental toxicity (OECD 421) is required in the REACH information strategy at the tonnage level 10-100 tpa, but is not included in the testing strategy in the TGD. REACH and TGD give different recommendation on how to evaluate and use the results from the OECD 421. According to REACH, positive results have to be confirmed in the developmental toxicity study (OECD 414), whereas the TGD states “data from OECD 421 may enable the rapporteur to identify a substance as toxic to reproduction (i.e. the test gives a clear “positive” result)”. The TGD also states that the screening test will not provide evidence for definitive claims of no effects.

It is not explained in REACH why positive results in the screening test have to be confirmed in further reproductive toxicity testing or why the developmental toxicity study is the “confirmatory” study. As clear “positive” results in the screening test, according to the TGD and the GHS criteria for classification, can be used to identify a substance as toxic to reproduction, it seems that the REACH requirement for confirmatory testing of positive results may lead to unnecessary use of experimental animals. In addition, the in vivo screening study may provide evidence of prenatal developmental toxicity effects, effects manifested during birth and the early postnatal period as well as effect on adult fertility. The developmental toxicity study provides results only on effects induced during prenatal development and manifested the day before birth and consequently perinatal effects and effects on adult fertility cannot be “confirmed” in the developmental toxicity study. The appropriate study for further investigations of such effects is a two-generation study, but this study is only to be proposed by the registrant if there are indications from a repeated dose toxicity study or structural relationship with a known reproductive toxicant at 10-100 tpa.

Ad 3) The potential human exposure is considered in both REACH and the TGD. In REACH, the screening test is not required at >10 t/a if “relevant human exposure can be excluded”. In contrast, the TGD recommends that widespread human exposure predicted difficult to control should lead to reproductive toxicity testing at >10 t/a instead of >100 t/a.

As the TGD does not consider the screening test it is somewhat difficult to compare these two approaches.

Ad 4) The sequence of testing using the two-generation study and the developmental toxicity study is different in the REACH proposal and the TGD. The REACH proposal requires developmental toxicity study at >10 t/a and only the two-generation study if there are indications from repeated dose toxicity studies or structural relationship. The TGD states that the first specific reproductive toxicity test should usually be the two-generation study followed by the developmental toxicity study.

Ad 5) The REACH proposal does not specify any investigations for developmental neurotoxicity effects using e.g. the OECD proposal for TG 426 Developmental Neurotoxicity Study, while the TGD states that the need for inclusion of a developmental neurotoxicity evaluation must be considered at the planning stage of the two-generation study and the developmental toxicity study and gives guidance on the issue. This means that the REACH information strategy in contrast to the testing strategy in the TGD does not require data that allows classification or risk assessment for developmental neurotoxicity.

Ad 6) The REACH proposal does not specify any use of the one-generation study (TG 415). The TGD similarly does not recommend the one-generation study, but mentions that in the rare event of the conduct of this study, a two-generation study will normally be required at 1000 t/a. However, if the one-generation test provides equivocal evidence of impaired fertility, further testing (with TG 416) for clarification should be initiated without further delay.

The existing criteria for classification and labelling of substances toxic to reproduction in Annex VI is shown in Appendix A, whereas the GHS-criteria is shown in Appendix B. The two sets of criteria are relatively similar – in general category 1, 2 and 3 in the EU criteria can be transferred to category 1A, 1B and 2 in the GHS-system, respectively. Classification of chemicals is generally based on epidemiological and animal data in both Annex VI and the OECD GHS. Data from structural relationship, (Q)SAR and in vitro studies are generally used only as supportive evidence for human and/or animal data.

For classification in category 2 and 3 in Annex VI, however, “Other relevant information” is also mentioned as a basis for classification. This has generally been used and was most probably meant to indicate that “other relevant information” may influence the decision on classification based on the results of animal studies. Consequently, the REACH information strategy will not provide sufficient data for classification purposes at the tonnage level <10 t/a, unless the use of the existing classification criteria are modified.

The REACH information strategy in contrast to the TGD testing strategy will not, as earlier mentioned, provide data that can be used for con-

sidering classification for developmental toxicity due to developmental neurotoxicity effects.

In conclusion, there are a number of potentially imports differences between the information requirements/testing strategies in the REACH proposal and the TGD. The information strategy in REACH seems in relation to the in vivo screening test to lead to unnecessary and even in some cases to irrelevant “confirmatory” testing. In addition, it does at some information levels not provide sufficient data for classification and risk assessment for reproductive toxicity.

Table 3. Summary of reproductive toxicity information strategies and data requirements in the REACH proposal and Technical Guidance Document (TGD) in comparison with the classification criteria in Annex VI and the Globally Harmonized System (GHS)

Reproductive toxicity Elements of information strategy	Information requirements and testing strategies		Classification criteria	
	REACH proposal	TGD, EU Technical Guidance on Risk Assessment	Annex VI	GHS
Use of existing human, animal and other data	In vivo tests are not required below 10 t/a. Above 10 t/a, tests are not needed if the substance is known to be a genotoxic carcinogen or a germ cell mutagen and appropriate risk management measures are implemented (see also Annex table C of this report).	Reproductive testing will not normally be required for germ cell mutagens and genotoxic carcinogens classified in Category 1 or 2. Testing requirements can be modified, depending on results of other toxicity studies. “Well reported... epidemiological studies... will contribute to the weight of the evidence.	Classification is mainly based on human and animal data. Sufficient epidemiological evidence showing causal relationship between human exposure and impaired fertility/toxic effects in the progeny leads to Repro Cat 1. Placing into categories 2 or 3 is primarily on the basis of animal data.	Classification is largely based on human and animal data and an assessment of the total weight of evidence. Sufficient evidence from humans or animals leads to Category 1A or 1B, respectively. Some evidence from humans or experimental animals leads to Category 2.
Physical and chemical properties	Not considered.	Physical and chemical data should be considered when developing test programme.	Not considered.	Not considered
(Q)SAR	For 10-100 t/a: The in vivo screening test for reproductive/developmental toxicity (OECD TG 421) is not required, if (Q)SAR estimates provide evidence that the substance may be a developmental toxicant.	Available information on SAR influence the decision whether to perform reproductive toxicity testing at 10 t/a or 100 t/a	Not considered	Adequate data can contribute to the weight of evidence.

Potential Exposure	For 10-100 t/a: In vivo tests are not required, if relevant human exposure can be excluded	Available information on potential human exposure influence the decision whether to perform reproductive toxicity testing at 10 t/a or 100 t/a	When effects have been demonstrated only at unrealistic high doses (in the test animals), classification in Cat 3 or no classification may be warranted.	General agreement on the concept of a limit dose above which adverse effects may be considered outside the criteria leading to classification. However, there was no agreement of a specified dose as a limit dose.
Known properties of the chemical group/category	For 10-100 t/a: The in vivo screening test for reproductive/developmental toxicity (OECD TG 421) is not required, if evidence from structurally related substances shows that the substance may be a developmental toxicant.	Testing requirements can be modified, depending on structural relationships with a known reproductive toxicant	Clear evidence in one animal species <u>and</u> chemical relationship to other known anti-fertility agent leads to classification in Cat 2.	Adequate data can contribute to the weight of evidence.
In vitro tests	For 10-100 t/a: The in vivo screening test for reproductive/developmental toxicity (OECD TG 421) is not required, if evidence from in vitro tests shows that the substance may be a developmental toxicant.	In vitro studies "may be available".	In vitro studies (e.g. in avian eggs) are regarded as 'supportive evidence' and would only exceptionally lead to classification in the absence of in vivo data.	Adequate data can contribute to the weight of evidence.
In vivo tests	<p><u>< 10 t/a:</u> No requirement for testing for reproductive toxicity</p> <p><u>≥ 10 t/a:</u> Screening study OECD 421 with one species and developmental toxicity study, i.e. OECD TG414. A positive result in the screening test shall be confirmed by a developmental toxicity study, i.e. OECD 414 (at first with one species). If there is indications of reproduction toxicity from a 90</p>	<p><u>< 10 t/a:</u> Case-by-case based on indications from other studies or SAR.</p> <p><u>≥ 10 t/a:</u> Two-generation study (TG 416) if there are indications from repeated dose study or structural relationship; or widespread human exposure. Developmental toxicity study (TG 414) if serious concerns from SAR and potential human exposure; or indications from two-generation study</p> <p><u>≥ 100 t/a:</u> Two-generation study and developmental</p>	Clear evidence from animal studies or "other relevant information" leads to classification with Repro Cat 2 or 3. Animal testing above the limit test (1000 mg/kg) may not be needed.	

	<p>day repeated dose study, the two-generation reproduction toxicity study should be proposed by the registrant.</p> <p><u>>100 t/a:</u> Developmental toxicity study OECD 414 at first with one species. If there is evidence of reproduction toxicity in the 28 or 90 day repeated dose study, two-generation reproduction toxicity study is required</p> <p><u>≥ 1000 t/a:</u> Two-generation study unless there is low toxicological activity, no systemic absorption and no significant human exposure.</p>	<p>toxicity study. May be delayed to 1000 t/a if there are low biological activity, no significant absorption and low concern in relation to exposure.</p> <p><u>> 1000 t/a:</u> Two-generation study and developmental toxicity study.</p>		
--	---	--	--	--

10. Conclusions on Human Health Endpoints

Information strategies or data requirements of the REACH proposal and the Technical Guidance Document, as well as the classification criteria of Annex VI (Directive 67/548/EEC) and GHS have been analysed. In this report three toxic endpoints were covered: acute toxicity, skin and eye irritation/corrosion and reproductive toxicity. The information strategies and classification criteria for the selected endpoints are inconsistent in many cases. Usually, in Annex VI, human data and in vivo test results are a prerequisite. Other types of data, such as physico-chemical properties or in vitro studies can sometimes be used as the basis or as supportive evidence for decision making in classification. REACH and TGD also differ in some parts in their testing strategies.

Some preliminary conclusions are drawn here, based on the analysis in the four previous chapters. Also some preliminary recommendations are made, some of which are further developed in step 2 of this project. Because the implementation of the REACH proposal could be supported by practical guidance and careful consideration of other legislation, we believe that our recommendations, although not completed at this stage, may be useful.

REACH Information Requirements and Classification Criteria

In several ways, the information requirements of the REACH proposal do not lead to the generation of sufficient data to allow for classification according to the classification criteria given in the Annex VI. According to REACH (and TGD) evaluation of many toxic endpoints can be based on (Q)SAR models/approaches, on structural similarity with known compounds, or on the *in vitro* test results. For substances produced or imported at volumes of 1-10 tonnes/a, mainly that kind of data is required according to the REACH proposal. However, this data can very seldom be used for classification (see tables 1-3 for details), as classification usually is based on existing human data and *in vivo* experiments. Therefore, classification for all endpoints for the low tonnage substances may not be possible.

For most endpoints above 10 t/a level (see appendix B), *in vivo* tests are a part of information requirements of the REACH proposal, thus enabling classification for many endpoints. However, if *in vivo* studies are exempted for on the basis of the availability of alternative data, such as (Q)SAR, structural similarity with known compounds, or *in vitro* results, classification will become more difficult. Although REACH does not require carcinogenicity studies at any tonnage level, it is stated in Annex V, point 8 that “Any other relevant physicochemical, toxicological and ecotoxicological information that is available shall be provided”. This will sometimes include epidemiological data, which is one of the corner stones of classification decision making for carcinogenicity categories 1 and 2.

When EU implements the GHS criteria, it should be assured that the criteria in EU are interpreted in a way to facilitate maximal use of *in vitro* data. If adequate decisions regarding classification cannot be made, other risk management measures could be applied, taking the endpoint of concern into consideration.

REACH and Risk Assessment

REACH information requirements for 1-10 t/a substances enable a preliminary hazard assessment for a few endpoints (skin and eye irritation/corrosion, sensitization, genetic toxicity). At that level, no test data on acute toxicity, repeated dose toxicity, reproduction toxicity will be required and consequently a complete hazard assessment and risk management cannot be done unless data is already available. Existing human data, such as case reports and/or epidemiological data may not be sufficient to fill this data gap.

Validated (Q)SAR models/approaches and *in vitro* methods would be helpful in screening substances for testing *in vivo*, in those cases where model predictions and/or *in vitro* data are inadequate as the basis for appropriate hazard evaluation and risk management. A number of activities concerning validation and regulatory acceptance have been initiated

in various fora. For an optimal implementation of REACH, it is considered necessary to strengthen development and validation activities of non-animal test methods. Another prerequisite for an optimal implementation of REACH is to develop suitable strategies on how such data can be used for regulatory decisions (classification & labelling, risk assessment, PBT-assessment, risk management), and if not, how the data in the most efficient way can be used in testing strategies.

Use of Existing Data

Essential information on the adverse effects of chemicals and on the exposure can sometimes be found in the open literature. Risk assessment of high production volume chemicals is based on published articles and reports and on confidential test reports. There are also several sources of unpublished data, such as the test data owned by industry, observations of occupational health personnel of industry, poison information centres and other registry data.

The use of existing data could be increased by e.g. listing the available data sources, developing advanced information search tools in networks. Those responsible of generation of data and of use of data should be involved in this exercise. The development of IUCLID as a global data portal/source is a step in this direction. Since the risk assessment process of REACH is primarily driven by the industry, the databases owned by the industry will be used more and made accessible also for the authorities. Accessibility of the data from poison information centres could be improved; analysis and reporting of those data on a regular basis would certainly be appreciated among the risk assessors and in the regulatory community. Furthermore, effective pre-analysis of existing data could be accomplished by developing intelligent search tools for IUCLID 5. The Chemicals Agency will have access to the whole database of the registered substances, which makes them the most logical and best equipped entity to perform this analysis.

(Q)SAR

In the three information strategies examined here, (Q)SAR models/approaches are considered but not in a systematic and coherent way. In the REACH proposal, the TGD and in the GHS, information obtained from (Q)SAR models/approaches are mentioned in several chapters, but without detailed guidance. In the Annex VI (Directive 67/548/EEC), for the toxic endpoints included in this report, the use of (Q)SAR is not considered in the specific criteria for classification.

Further development and validation of (Q)SAR models/approaches and guidance on reliability and limitations is needed.

In the future, (Q)SAR models/approaches may be useful for screening and prioritization of those chemicals, which are well covered by these approaches. Attempts to collect easily available and validated modelling

tools and software are in progress. Emphasis is put on models/approaches, which by experience have proven useful for evaluation of chemicals in a regulatory context.

It is well known by regulators that evaluation of test data require expert knowledge. This is also the case for evaluation of information obtained by use of (Q)SAR models/approaches. Even though the two types of expert knowledge have some common grounds, specific expert knowledge regarding evaluation of information obtained by use of (Q)SAR models/approaches is also needed. Such type of expert knowledge is currently not commonly available in industry or by regulators. Therefore new initiatives have been started for capacity building in this area, because this is seen as an essential element of the future successful implementation of REACH.

For chemicals with few test data (low tonnage chemicals, under REACH), adequate positive indications from validated (Q)SAR models/approaches should be considered sufficient for classification and labelling or to trigger further testing at a lower tonnage level than required in REACH. Guidance to be developed in future should contain approaches describing how such information may be used in lower tier regulatory risk assessment procedures. For chemicals used in large quantities, positive evidence from (Q)SAR models/approaches could be used for classification and risk assessment and/ or as appropriate to decide and plan the next testing level.

In Vitro Tests

There are toxic effects and toxicity mechanisms which can be studied in cytotoxicity assays or with ex vivo techniques. When validated and formally approved, cytotoxicity assays or ex vivo techniques can be used to limit the number of those chemicals, which would otherwise be studied in expensive and time consuming in vivo tests. It would greatly help to achieve the ambitious goals of the REACH if more reliance were given to well-characterised/validated in vitro methods.

In vitro tests can be used to support existing data (including e.g. available animal test data, case reports, poisoning data and physical and chemical properties) and further in vivo tests. Non-validated in vitro tests could also be used on a case by case basis. However, the limitations of non-validated tests should be carefully considered.

For the screening phase of the information strategies as well as for toxicokinetic and mechanistic studies, in vitro tests should be used, when scientifically justified. Development of test protocols and funding of validation studies are necessary.

Exposure-based vs. Tonnage-based Testing

Other elements of an information strategy than the tonnage based test requirements of REACH will often determine whether an *in vivo* test is actually necessary or not.

The tonnage-based information strategy has been questioned (e.g. ref. ATLA), because production volume can be a poor predictor of exposure or risk caused by a chemical. The substance's physico-chemical properties, the use pattern and the controls in place may be more important risk determinants than the production volume when assessing risks to human health. Reliable risk assessment and classification are necessary for those substances, which cause worker or consumer exposure, independent of the tonnage level. Whether the substance is handled manually, is bound to a matrix, passes in segregated processes or is merely a short-lived intermediate it may lead to significant exposure.

That is why the information strategy of REACH includes consideration of exposure at tonnage levels above 10 tpa where risk assessment is required for dangerous chemicals.

At higher tonnage levels where REACH does not prescribe specific tests for long term toxicity it is suggested that the intensity, frequency and duration of exposure as well as considerations concerning exposed populations and relevant hazard indications should be taken into account when chemicals are prioritized for certain *in vivo* tests (e.g. tests for cancer, developmental neurotoxicity, immunotoxicity).

Exposure can be measured or estimated using special software. Freely available software, such as EASE and EUSES has been used in the EU ESR risk assessment programme previously. Expert judgement of the modelling results is required.

One of the challenges under REACH will be how well the information flow concerning use of the registered chemicals up and down the supply chain will work, because the uses of chemicals are determining the exposure scenarios and thus influence the basis for the chemicals safety assessment and subsequent risk management measures.

Negative and Positive Results and Further Testing

In the existing information strategies, further testing can be triggered either by negative or positive test results. The scientific reasoning behind the decision to test or not to test should be transparent and acceptable in this regard. Tests, which are considered to provide sufficient information for hazard assessment or classification purposes should not usually lead to further testing, except specific cases, such as mechanistic studies, which can lead to reduction of further testing later. At the lower “tier levels” it might be a reasonable approach that positive test results, when sufficiently reliable, are followed by risk management measures and not additional tests, especially if it is unlikely that the further tests will provide significant improvement in the weight of evidence assessment of earlier tests.

References

- Combes R., M. Barratt & M. Balls (2003). An overall strategy for the testing of chemicals for human hazard and risk assessment under the EU REACH system. *ATLA* 31, 7-19, 2003.
- Commission Directive 93/67/EEC laying down principles for assessment of risks to man and the environment of substances notified in accordance with Council Directive 67/548/EEC. *OJ No L 227*, 08.09.93, pp.9-18.
- Commission Directive 95/36/EC amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. *OJ No L 172*, 22.07.95, pp.8-20.
- Commission Directive 96/12/EC amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market. *OJ No L 65*, 15.03.96, pp.20-37.
- Commission of the European Communities (2003). Proposal for a Regulation of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency and amending Directive 1999/45/EC and Regulation (EC) {on Persistent Organic Pollutants}. COM(2003) 644 final.
- Commission Regulation (EC) No 1488/94 laying down the principles for the assessment of risks to man and the environment of existing substances in accordance with Council Regulation (EEC) No 793/93. *OJ No L 161*, 29.06.94, pp. 3-11.
- Council Directive 91/414/EEC concerning the placing of plant protection products on the market. *OJ No L 230*, 19.08.91, pp.1 ff.
- Council Directive 92/32/EEC amending for the seventh time Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *OJ No L 154*, 05.06.92, pp.1-29.
- Council Regulation (EEC) No 793/93 on the evaluation and control of the risks of existing substances. *OJ No L 84*, 05.04.93, pp.1 ff.
- DG SANCO (2002a). Guidance document on aquatic ecotoxicology in the context of the Directive 91/414/EEC. Sanco/3268/2001 rev.4 (final).
- DG SANCO (2002b). Guidance document on terrestrial ecotoxicology under Council Directive 91/414/EEC. Sanco/10329/2002 rev.2 (final).
- European Commission (2001). White Paper - Strategy for a future Chemicals Policy. COM(2001) 88 final.
- European Commission (2000). Technical notes for guidance in support of Directive 98/8/EC concerning the placing of biocidal products on the market. Guidance on data requirements for active substances and biocidal products. Final draft, version 4.3.2.
- European Commission (2003). Technical Guidance Document on risk assessment in support of Directive 93/67/EEC, COM Regulation (EC) 1488/94 and Directive 98/8/EC. Part II (Environmental risk assessment). EUR 20418 EN/2.
- European Commission (2004). Manual of decisions for implementation of the sixth and seventh amendments to Directive 67/548/EEC on dangerous substances (Directive 79/831/EEC and 92/32/EEC). EUR 20519 EN.
- European Parliament & the Council (1998). Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. *OJ No L 123*, 24.04.98, p.1-63.
- OECD (2001). Harmonised integrated classification system for human health and environmental hazards of chemical substances and mixtures. ENV/JM/MONO(2001)6.
- OECD (2003). Manual for investigation of HPV chemicals. www.oecd.org
- OECD Test guidelines. www.oecd.org
- Pedersen F., J. de Bruijn, S. Munn & K. van Leeuwen (2003). Assessment of additional testing needs under REACH – Effects of

(Q)SARs, risk based testing and voluntary industry initiatives. European Commission, Joint Research Centre, Institute for Health and Consumer Protection. Report EUR 20863 EN, 36 pp.+annexes (<http://ihcp.jrc.it/>).

United Nations (2003). Globally harmonized system on classification and labeling of chemicals (GHS). United Nations, New York and Geneva, ISBN 92-1-116840-6, 450 pp.

Acronyms

GHS	Globally Harmonized System of Classification and Labeling of Chemicals (UN SG GHS)
GLP	Good Laboratory Practise
HPV	High Production Volume (Chemicals)
OECD	Organisation of Economic Co-operation and Development
QSAR	Quantitative Structure Activity Relationship
REACH	Registration, Evaluation and Authorisation of Chemicals, COM 2003 0644 (03)
RIP	Reach Implementation Project
SAR	Structure Activity relationships
SPR	Structure Property Relationship
TG	Test Guideline approved by the OECD, specified by number
TGD	Technical Guidance Document on Risk Assessment, by the European Commission, April 2003

Appendix A Overview of Environmental Test Requirements or Needs under Various Legislation

Ecotoxicology	REACH	Existing substances (prioritised)	New substances	C & L (incl. GHS)	PBT/vPvB assessment	Biocides	Pesticides	OECD HPVC (prioritised)
Physicochemical properties								
Log Pow	When: >1 tpa Except: Inorganics	When: >1000 tpa	When: >0.1 tpa	When: Needed for C&L purpose unless BCF data available	When: Screening for bioaccumulation in marine species	When: Always	When: Always	When: >1000 tpa
Aquatic toxicity								
Short-term toxicity to Daphnia (crustaceans)	When: >1 tpa Except: Sw<10µg /L MW>800	When: >1000 tpa	When: >1 tpa	When: Needed for C&L purpose	When: Screening for high toxicity	When: Always	When: Always For insecticides, an additional invertebrate (insect)	When: >1000 tpa
Growth inhibition on algae	When: >10 tpa Except: Sw<10µg /L MW>800	When: >1000 tpa	When: >1 tpa	When: Needed for C&L purpose	When: Screening for high toxicity	When: Always	When: Always For herbicides, an additional sp.	When: >1000 tpa
Short-term toxicity to fish	When: >10 tpa Except: Sw<10µg /L MW>800	When: >1000 tpa	When: >1 tpa	When: Needed for C&L purpose	When: Screening for high toxicity	When: Always	When: Always	When: >1000 tpa
Activated sludge respiration inhibition	When: >10 tpa Except: Sw<10µg /L RB					When: Not specified	When: Use can give rise to adverse effects on STP	
Long-term toxicity to Daphnia (or appropriate invertebrate)	When: >100 tpa & Risk Sw<1mg/L	When: Risk & Daphnia most sensitive in short-	When: >10/100 tpa	When: For declassifying R52/53 or R53	When: Suspicion on chronic toxicity to marine	When: Likely exposure of aquatic environment	When: Always Except: Continued or	When: Exposure and concern for long-term

Ecotoxicology	REACH	Existing substances (prioritised)	New substances	C & L (incl. GHS)	PBT/vPvB assessment	Biocides	Pesticides	OECD HPVC (prioritised)
	Except: MW>800 No exposure	term test		For declassifying Chronic II or III or IV (cf. GHS)	species	(appropriate invertebrate)	repeated exposure is unlikely	effects using most sensitive species
Long-term toxicity to fish	When: >100 tpa & Risk Sw<1mg/L Bioaccumulative (FELS) Except: MW>800 No exposure	When: Risk & fish most sensitive in short-term test	When: >10/100 tpa	When: For declassifying R52/53 or R53 For declassifying Chronic II or III or IV (cf. GHS)	When: Suspicion on chronic toxicity to marine species	When: Likely exposure of aquatic environment	When: Always Except: Continued or repeated exposure is unlikely	When: Exposure and concern for long-term effects using most sensitive species
Nitrification inhibition	When: >10 tpa & Microbial inhibitors							
Bacterial inhibition		When: >1000 tpa	When: >1 tpa & Before biodegradation test if biodegradation may be affected	When: Needed when no degradation in a biodegradation test		When: Always		
Aquatic plant toxicity w. Lemna sp.				When: Alternative to algae toxicity test		When: Antifouling substances	When: For herbicides	
Degradation								
Ready biodegradability	When: >10 tpa Except: Inorganics	When: >1000 tpa	When: >0.1 tpa	When: Needed for C&L purpose	When: Screening for marine persistence	When: Always	When: Always Except: Not required for C&L	When: >1000 tpa
Simulation surface water	When: >100 tpa & Risk Except: Sw<10µg/L RB	When: Risk	When: >10/100 tpa & Sufficient degradation is not proved	When: For declassifying R52/53 or R53 For declassifying Chronic II or III or IV (cf. GHS)	When: Suspicion on marine persistence		When: Always (water/sediment study) Except: No exposure of surface water	
Simulation soil	When: >100 tpa &	When: Risk	When: >10/100 tpa &	When: Alternative to			When: Always	

Ecotoxicology	REACH	Existing substances (prioritised)	New substances	C & L (incl. GHS)	PBT/vPvB assessment	Biocides	Pesticides	OECD HPVC (prioritised)
	Sorption Risk Except: RB No exposure		Sufficient degradation is not proved	simulation surface water			Except: No exposure	
Simulation sediment	When: >100 tpa & Sorption Risk Except: RB No exposure	When: Risk	When: >10/100 tpa & Sufficient degradation is not proved	When: Alternative to simulation surface water				
Confirmatory biodegradation rates	When: >1000 tpa & Risk							
Hydrolysis	When: >10 tpa Except: Sw<10µg /L RB	When: >1000 tpa	When: >1 tpa Except: RB	When: Considering as readily or rapidly degradable (incl. degradation products assessed as not hazardous to the aquatic environment). (cf. GHS)		When: Always	When: Always	Except: Substances w. structures resistant to hydrolysis
Identification of degradation products	When: >100 tpa Except: RB			When: Rapid hydrolysis.		When: NRB	When: Always as part of soil degradation study	
Inherent biodegradability		Not recommended				When: NRB & where appropriate; however not recommended		
Phototransformation in water		When: >1000 tpa				When: Always	When: Always	When: >1000 tpa
Estimation of phototransformation in air (QSAR)		When: >1000 tpa				When: Always		
Phototransformation in air		When: Serious risks				When: Risks to atmospheric	When: Always Except:	

Ecotoxicology	REACH	Existing substances (prioritised)	New substances	C & L (incl. GHS)	PBT/vPvB assessment	Biocides	Pesticides	OECD HPVC (prioritised)
						environment	No exposure	
Stability in soil								
Active sludge simulation		When: Inhibitory to micro-organisms				When: Emission to STP		
Biodegradation in seawater						When: Likely exposure of marine waters		
Anaerobic biodegradation						When: Likely exposure of anaerobic compartments	When: Always Except: No exposure to anaerobic conditions	
Fate and behaviour								
Adsorption/desorption	When: >10 tpa Except: Low sorption Decomposes rapidly	When: >1000 tpa	When: >1 tpa			When: Always	When: Always Except: No exposure	SAR or experimental
Potential for bioconcentration in aquatic organisms						When: Always		
Bioconcentration in fish (and/or appropriate invertebrate)	When: >100 tpa Except: Log Pow<3 MW>800 No exposure		When: >10/100 tpa	When: For C&L purpose when log Pow ≥ 3 (≥ 4 in GHS) or cannot be determined	When: Suspicion on bioaccumulation in marine species	When: Antifouling substances with a potential for sec. pois. (incl. appropriate invertebrate)	When: Log Pow>3 Except: No exposure DT90<10 d	
Further adsorption/desorption	When: >100 tpa Except: Low sorption Decomposes rapidly		When: >10/100 tpa & Depends on previous results			When: Direct release to soil, Risks to soil, Leaching potential	When: For relevant metabolites	
Further fate and behaviour	When: >1000 tpa		When: >1000 tpa			When: Risk to		

Ecotoxicology	REACH	Existing substances (prioritised)	New substances	C & L (incl. GHS)	PBT/vPvB assessment	Biocides	Pesticides	OECD HPVC (prioritised)
	& Risk					specific environment or compartment		
Mobility in soil			When: >1000 tpa			When: Leaching potential and risk to ground-water	When: Always Except: Reliable adsorption data available	
Effects on terrestrial organisms								
Short-term toxicity to earthworms	When: >100 tpa Except: No exposure	When: Risk based on EP from aquatic data	When: >10/100 tpa			When: Exposure is likely	When: Exposure is possible	When: Significant exposure
Effects on soil micro-organisms	When: >100 tpa Except: No exposure	When: Risk based on EP from aquatic data				When: Exposure is likely	When: Exposure is possible (microbial processes)	When: Significant exposure
Short-term toxicity to plants	When: >100 tpa Except: No exposure	When: Risk based on EP from aquatic data	When: >10/100 tpa			When: Exposure is likely	When: Potential risk	(>1000)
Long-term toxicity to earthworms	When: >1000 tpa & Risk Except: No exposure	When: Risk based on short-term tests					When: DT90>36 5d, Appl.>6, TER<10 Except: DT90<10 0d & Appl.<3	
Long-term toxicity to soil invertebrates	When: >1000 tpa & Risk Except: No exposure	When: Risk based on short-term tests					When: 100d<DT 90<365d Except: Litter bag test available	
Long-term toxicity to plants	When: >1000 tpa & Risk Except: No exposure	When: Risk based on short-term tests					When: Risk (field or semi-field studies)	
Honeybees						When: For insecti-	When: Exposure is likely	

Ecotoxicology	REACH	Existing substances (prioritised)	New substances	C & L (incl. GHS)	PBT/vPvB assessment	Biocides	Pesticides	OECD HPVC (prioritised)
						cides, acaricides, etc.		
Non-target (beneficial) arthropods							When: Exposure is possible	
Effect on sediment organisms								
Long-term toxicity to sediment organisms	When: >1000 tpa & Risk	When: Risk based on short-term tests or EP from aquatic tests				When: For antifouling substances when exposure and effect is likely	When: >10% in sediment after 14d, Daphnia/-insect NOEC <0.1 mg/L	
Effects on birds								
Acute toxicity to birds			When: >1000 tpa			When: For rodenticides, molluscicides, insecticides, acaricides, etc.	When: Always Except: No exposure	When: Post-SIDS stage
Long-term toxicity to birds	When: >1000 tpa Except: No exposure					When: For rodenticides, molluscicides, insecticides, acaricides, etc.	When: Always Except: Exposure in breeding season is unlikely	

Appendix B Overview of Human Health Test Requirements or Needs under Various Legislation

Overview of the tonnage based information/test requirements of various legislations (and regulatory recommendations). In the Annexes of the REACH proposal, specific rules have been given for adaptation of information requirements; these rules are not indicated in this table in detail, some examples are given in the footnotes below.

Acute toxicity	REACH	Existing substances, Council Regulation No 793/93 (Annex III)	New substances	OECD HPV
Acute oral toxicity with toxic class method, up-and down method or with fixed dose procedure	> 10 tpa	> 1000 tpa ¹⁾	> 10 kgpa and the substance is not a gas	> 1000 tpa
Acute dermal toxicity	> 10 tpa, depending on e.g. skin contact and dermal absorption	> 1000 tpa ¹⁾	> 1 tpa, depending on the nature of the substance and the likely route of human exposure	> 1000 tpa, dependent upon the most important route of human exposure and physical-chemical properties of the substance
Acute inhalation toxicity	> 10 tpa, depending on vapour pressure, particle size, aerosol formation.	> 1000 tpa ¹⁾	> 10 kgpa and the substance is a gas	> 1000 tpa, gases and vapours; dependent upon the most important route of human exposure and physical-chemical properties of the substance
Irritation and corrosion	REACH	Existing substances, Council Regulation No 793/93 (Annex III)	New substances	OECD HPV
In vitro skin irritation	> 1 tpa ³⁾			Not required. Reported when available.
In vitro eye irritation	> 1 tpa ³⁾			Not required. Reported when available.
In vitro skin corro-	> 1 tpa ³⁾			Not required.

sion				Reported when available.
In vivo skin irritation	> 10 tpa ³⁾	> 1000 tpa ¹⁾	>100 kgpa	Not required. Reported when available.
In vivo eye irritation	> 10 tpa ⁴⁾	> 1000 tpa ¹⁾	>100 kgpa	Not required. Reported when available.
Sensitization				
Skin sensitization		> 1000 tpa, test not specified	>100 kgpa	Not required. Reported when available.
LLNA	> 1 tpa ⁵⁾			Not required. Reported when available.
Repeated dose toxicity				
28 days oral toxicity study	> 10 tpa ⁶⁾	> 1000 tpa, test not specified	>1 tpa, in absence of contra-indications the oral route is preferred	> 1000 tpa, oral, dermal and inhalation routes and respective test guidelines are listed.
90 days oral toxicity study	> 100 tpa ⁷⁾			
Long-term repeated toxicity study (≥12 months)	> 1000 tpa ⁹⁾			
Toxicity to reproduction and development				
Screening test for reproduction toxicity	> 10 tpa ²⁾	> 1000 tpa, test not specified	> 1 tpa	Not required. Reported when available.
Developmental toxicity study	> 10 tpa, if the screening test is positive, and > 100 tpa ⁸⁾			> 1000 tpa
One-generation reproduction toxicity study				> 1000 tpa, either one- or two-generation reproduction toxicity study is required.
Two-generation reproduction toxicity study	> 100 tpa ⁸⁾ , if there is evidence from reproduction toxicity in repeated dose studies > 1000 tpa			> 1000 tpa, either one- or two-generation reproduction toxicity study is required.

1) According to the Technical Guidance Document (TGD), existing data is evaluated before in vivo testing, see table 1 and 2 for details.

2) No in vivo tests are needed, if sufficient information is obtained from QSAR, from evaluation of structurally similar compounds or from the in vitro studies or when humans are not exposed to the substance.

3) These tests are not required e.g. when the substance corrosive or toxic dermally, or when the substance is strong acid or base.

4) The test is not required e.g. when the substance corrosive or classified skin irritant, or when the substance is strong acid or base.

5) Test is not required when existing data is sufficient for the classification, when the substance corrosive, toxic or causing irritation dermally, or when the substance is strong acid or base.

- 6) The study is not required when there is a sub-chronic (90 days) or chronic toxicity study available or when human exposure can be excluded. Rules for selection of an appropriate route of exposure are given as well as possible indications of further studies.
- 7) The study is not required if severe toxicity is observed in the 28 days study, when chronic toxicity study available or the substance is unreactive, insoluble and not inhalable and no toxicity was seen in a 28 days limit test, particularly if such a pattern is coupled with limited human exposure. Rules for selection of an appropriate route of exposure are given as well as possible indications of further studies.
- 8) These tests are not required, if the substance is a genotoxic carcinogen or a germ cell mutagen. Most appropriate route, regarding the likely human exposure, should be selected.
- 9) The test may be required, when other repeated dose studies have shown severe toxicity but evidence is insufficient or when dangerous properties may have gone undetected in a 90 days study.