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European Experience in Chemicals Management: Integrating Science into Policy†

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The European Union (EU) adopted the first legislation on chemicals management in 1967 with the Dangerous Substances Directive (DSD). Over time the underlying concepts evolved: from hazard identification over risk assessment to safety assessment. In 1981 a premarketing notification scheme was introduced. Approximately 10 years later a risk assessment program started for existing substances following a data collection and prioritization exercise. Integration of science into EU chemicals legislation occurred via several technical committees managed by the European Chemicals Bureau (ECB) and resulted in the Technical Guidance Document on Risk Assessment (TGD), which harmonized the risk assessment methodology. The TGD was revised several times to adapt to scientific developments. The revision process, and the risk assessments for new and existing substances, led to scientific research on chemical risk assessment and thus increased in complexity. The new EU chemicals policy REACH (Registration, Evaluation, Authorization and Restriction of CHemicals) builds on previous experiences and aims to further enhance health and safety. REACH places the burden of proof for chemical safety on industry focusing on managing risks. REACH formalizes the precautionary principle. Furthermore, it underlines a continued scientific underpinning in its implementation, also via stakeholder involvement, and a focus on aligning with international fora.

Introduction

Legislation addressing industrial chemicals in the European Union (EU) evolved from hazard identification in the Dangerous Substances Directive 67/548/EEC (DSD) (*1*), via risk assessment (*2, 3*) to safety assessment in the REACH regulation (*4*).

Earlier publications have reviewed EU chemicals legislation. Bodar et al. (2003) evaluated the results of the then ongoing EU program on the risk assessment for existing substances (*5*), while Gebel et al. (2009) presented an overview of EU chemicals legislation, discussing the risks and changes of REACH in the context of the limitations of the previous legislation (*6*). An overview of chemicals management in the EU focusing on REACH was given by Van Leeuwen et al. (2007) (*7*).

We will present an overview of developments and achievements of the past and present environmental EU policy on chemicals management, focusing on risk assessment and on the integration of science into policy to show how science, and more specifically regulatory science, was incorporated into the EU regulatory framework on chemicals. We focus on industrial chemicals, excluding pesticides, biocides, and pharmaceuticals for which other EU legislation applies. In the early 1990s, the increased technical-scientific needs for implementing the chemicals legislation triggered the creation of the European Chemical Bureau (ECB) within the European Commission's Joint Research Centre (JRC). This created a focal point for integrating scientific knowledge into policy implementation and development.

REACH redefined the EU chemicals policy to address problems with the implementation speed, management, and diversity of the legal base built up over the preceding 40 years as well as building on the more operational and successful parts and methodologies. REACH shifts the responsibility for chemical safety from the Member States' authorities to the chemicals industry by emphasizing upfront risk management by industry and thereby changes the way risks are assessed. We specify the practical and scientific consequences that the REACH paradigm shift triggered regarding the assessment and management process.

Historical Perspective of EU Chemicals Legislation

The control of industrial chemicals through legislation started in the 1960s with the Dangerous Substances Directive (DSD) (*1*); an overview of the chemicals legislation is given in Figure 1.

The DSD introduced a classification and labeling system (C&L) for substances applying three means for hazard communication: standard hazard symbols, supported by risk and safety phrases. The system was complemented in 1988 with the Dangerous Preparations Directive (DPD) (*8*), resulting in a system where all marketed substances and preparations in the EU were classified and labeled. Classification criteria were established, first for physicochemical and health hazards and later also for environmental hazards. Hazard classification did cover hazard identification and also hazard characterization (with respect to potency considerations). A substance or preparation meeting the criteria was considered to be dangerous, an important notion as this would trigger obligations under downstream legislation. Substances or groups of substances with an EU harmonized C&L were listed in Annex I of the DSD and Annex I was extended via so-called Adaptations to Technical Progress (ATP) of the DSD. The EU Member States were responsible for harmonized C&L, and the Technical Committee on Classification and Labeling (TC C&L) discussed C&L proposals and agreed proposals were published as ATPs; 31 ATPs were published containing over 4000 entries in Annex I. For substances without a harmonized C&L, industry was obliged to self-classify and to provide this information via the Safety Data Sheet. In 2009 a new regulation on classification, labeling, and packaging of substances and mixtures (CLP Regulation) entered into force (*9*). The CLP Regulation implements the

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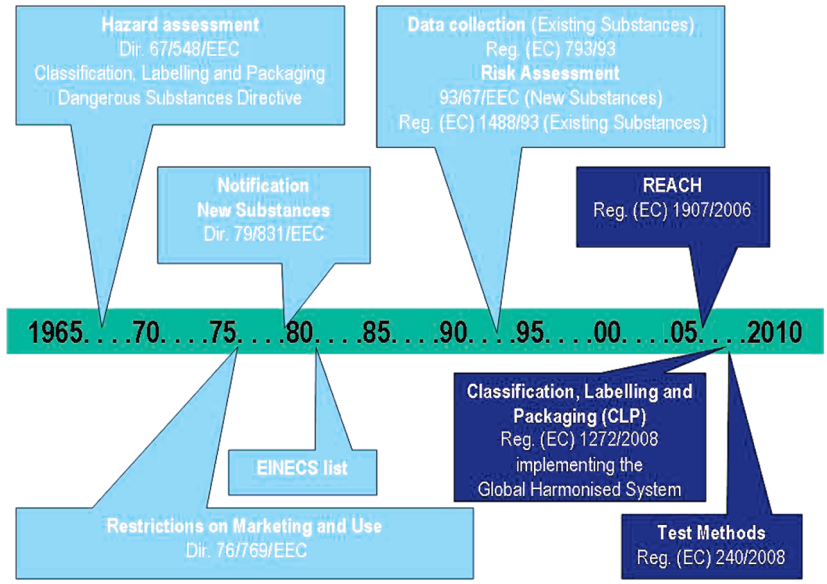

FIGURE 1. Development of EU chemicals legislation between 1967 (Dangerous Substances Directive) and 2008 (Test Methods Regulation).

United Nations' Globally Harmonised System (GHS) for classification and labeling (*10*) and will stepwise replace the DSD and DPD, where Annex VI of the CLP replaces Annex I of the DSD. The GHS classification criteria for health and environmental hazards are to a large extent based on the EU system.

The sixth amendment of the DSD from 1979 (*11*) introduced a premarketing notification scheme with mandatory data requirements for new substances, defined as substances imported or manufactured in the EU for the first time after September 18, 1981. A dossier was required providing general information on the substance (e.g., on production process and uses), and test results on physicochemical, toxicological, and ecotoxicological properties. Data requirements increased stepwise with the quantity placed on the market, starting from 10 kg to more than 1000 tonnes per year per manufacturer or importer. Information was exchanged between EU Member States via the New Chemicals Database (NCD). Proposals for classification and labeling had to be submitted. The seventh amendment of the DSD (*12*) introduced an obligation to perform a risk assessment for new substances (*3*). The European LIst of Notified Chemical Substances (ELINCS) provided a periodically updated inventory of new substances, comprising in total 5287 substances (*13, 14*). This notification scheme has been replaced by REACH.

The introduction of formal data requirements required standardized and agreed test methods. These were laid down in Annex V of the DSD and divided into methods for the determination of physical-chemical properties, toxicity, and ecotoxicity. With the entry into force of REACH, Annex V of the DSD was replaced by separate EU legislation: Regulation (EC) 440/2008, called the Test Methods Regulation (TMR) (*15*) currently including nearly 100 test methods. The test methods development is still carried out in close cooperation with the Organization for Economic Co-operation and Development (OECD) test guidelines program, ensuring mutual acceptance.

In 1993 Regulation 793/93/EEC (the Existing Substances Regulation (ESR)) introduced a comprehensive framework for evaluation and control of existing substances (*16*). An existing substance in the EU was defined as listed in the European INventory of Existing Commercial chemical Substances (EINECS), containing substances that were reported to be on the market in the EU between first January 1971 and 18th September 1981. EINECS, being a 'closed' list, contains in total 100,204 substances (*17*). ESR sets the frame for a rational evaluation of existing substances in line with the OECD existing chemicals program (*18*) and Chapter 19 of the Agenda 21 Rio Declaration, adopted at the United Nations Conference on Environment and Development in 1992 (*19*). These programs, including ESR, were guided by the policy principle of sustainability. Before ESR, marketing of existing substances was not subject to testing and assessment obligations, and available information was scattered and mostly insufficient to assess and control them effectively and thus guarantee sustainable use.

The ESR scheduled the evaluation of existing substances in four phases:

Phase 1: Data Collection. The ESR first dealt with High Production Volume Chemicals (HPVCs), imported or produced in the EU between 23rd March 1990 and 23rd March 1994 in quantities exceeding 1000 tonnes per year per manufacturer or importer, who had to submit their available data electronically. In a second data collection step, companies which produced or imported existing substances in quantities between 10 and 1000 tonnes per year (Low Production Volume Chemicals (LPVCs)) were required to submit a reduced data set in 1998. All data were stored in a dedicated database, IUCLID. Some 2500 HPVCs and 30,000 LPVCs were reported. Nonconfidential information submitted for these substances was published as IUCLID Data Sheets as a compact disc and via the European chemical Substances Information System (ESIS) (*20*).

Phase 2: Priority Setting. Priority substances were identified using a priority setting tool, the EU Risk RAnking Method (EURAM), which was developed by the ECB in consultation with stakeholders (industry, Member State experts, Non-Governmental Organizations (NGOs), the European Commission, non-EU experts, and other academic experts). It ranked substances according to potential risk based on exposure and effect modeling (*21*). Since 1994, four priority lists were published, listing 141 priority substances.

Phase 3: Risk Assessment. Priority substances underwent an in-depth risk assessment covering the risks posed to man and the environment. The Member States acted as scientific 'rapporteurs' (RMS), preparing risk assessment reports (RARs) describing the outcome of the risk assessment process for each priority substance. RARs were discussed/peer-reviewed by the Technical Committee for New and Existing Substances

(TC NES) with the objective to reach consensus on the conclusions. All stakeholders participated in the TC NES, which was chaired by the ECB. ESR stipulated three possible conclusions of the risk assessment:

(i) there is need for further information and/or testing;

(ii) there is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already, or

(iii) there is a need for limiting the risks; risk reduction measures which are already in place shall be taken into account.

The draft RARs were peer reviewed by an independent scientific body set up by the Commission, the Scientific Committee for Toxicology, Ecotoxicology and the Environment (CSTEE), and later the Scientific Committee on Health and Environmental Risk (SCHER) (*22*). Results from this peer review were considered when deciding on the need for risk reduction.

Phase 4: Risk Reduction. Substances of concern, i.e. substances with a conclusion (iii), were subject to risk reduction measures (RRM) to limit exposure. For more than 40 priority substances RRM were applied according to the degree of concern, determined from the risk assessment conclusion of a particular exposure and/or effect. In severe cases, Directive 76/769/EEC (*23*) would be applied to restrict marketing and use of a substance. This Directive has also been replaced by REACH.

In total 137 RARs were prepared by the RMSs. For approximately 80 priority substances the whole process was finalized before REACH entered into force, leading to a communication by the Commission on the RRMs and the results of the risk assessments and risk reduction strategies. The RARs were published via ESIS (*20*). When REACH replaced ESR, evaluations not finalized were handed over to the European Chemicals Agency (ECHA).

PBT Assessment. After the introduction of the ESR it became clear that substances which are persistent, bioaccumulative, and toxic (PBT) or very persistent and very bioaccumulative (vPvB) pose a particular challenge to chemicals safety management. This concern was also internationally recognized by organizations like OSPAR (Oslo Paris Convention for the protection of the marine environment of the North-East Atlantic) and the United Nations Economic Commission for Europe because of the detection of such substances in remote regions like the Arctic. A guiding policy principle appearing from this concern was the precautionary principle. An EU interim strategy for management of PBT and vPvB substances was developed based on the precautionary principle (*24*).

Key steps of this interim PBT strategy were as follows: i) development of PBT and vPvB criteria and testing strategies, ii) identification of potential PBT or vPvB substances using screening data and screening estimation techniques for substances for which relevant data was missing, and iii) verification of PBT or vPvB properties by additional testing using the available legislative possibilities under ESR and the DSD. The second step resulted in a list of 125 existing substances, being candidates for identification as PBT or vPvB (*25*). A similar number of new substances above 10 tonne/year were assessed (unpublished due to business confidentiality). A subgroup, the PBT Working Group (PBT WG) on identification of PBT and vPvB substances, was established under the TC NES with the task to perform a case-by-case evaluation of the identified candidates and to give recommendations on the most appropriate follow-up actions. Before REACH entered into force conclusions had been reached for 90 existing substances, of which 27 were identified as PBT and/or vPvB. For the remaining 35 substances additional information was required. These evaluations and those of the new substances were handed over to ECHA. For all existing substances on the PBT candidate list, so-called Summary Fact Sheets were published via ESIS (*20*).

Despite the successful development and global acceptance of 137 risk assessment reports for existing chemical substances and the procedures around them involving all stakeholders, the process was time-consuming and completion for all existing substances within a realistic time scale was impossible. This was closely connected to

- the Member State authorities led the assessment process but frequently lacked knowledge on how substances were concretely used;

- dialogue with industry took place via manufacturers and importers, so often details of downstream use was lacking;

- limited information on inherent chemical-physical and toxicological properties.

This led to the requirement of Registration under REACH that asks industry upfront to collect and generate data on uses, exposures, and inherent properties and, where appropriate, conduct a chemical safety assessment based on these data showing how risks can be controlled throughout the chemical life cycle. This must be documented in a Registration Dossier to be submitted to ECHA within deadlines depending on manufacturing/import volume and other considerations. The authorities will check a fraction of the registrations in the REACH Evaluation procedure.

Integrating Science into the Previous EU Chemicals Legislation: Process and Results

Regarding the integration of science into chemicals policy, the notion of regulatory science in contrast to academic or research science is relevant (*26*). The objective of regulatory science is to support regulatory requirements. For ESR this is, for example, a decision on the outcome of the risk assessment in terms of the three conclusions mentioned before and to provide reliable and scientifically sound information to decision makers. In regulatory science, predictive certainty is required by the regulators, and the time frame is determined and driven by regulatory and political processes. Regulatory science may react to scientific developments, for example measurements in the Arctic leading to the notion of PBT substances and persistent organic pollutants leading to establishment of the precautionary principle. Regulatory demands often lead to a 'forced' decision on scientific issues, while the academic debate continues. This 'forced' decision making process, in fact dealing with uncertainty, may impede scientific progress as the regulatory debate has ended. On the other hand it also forces the regulatory scientist to take a position and often leads to follow-up research to refine, substantiate, or falsify the previously 'closed' decision.

The integration of science into EU chemicals legislation occurred via the technical committees through the following mechanisms: i) initiatives from the EU Commission, Member States, or other stakeholders such as industry or NGOs relating to guidance development; ii) spin-off from the discussions on the risk assessments for new and existing substances having identified unresolved scientific issues; and iii) in-house activities of the ECB, for example QSAR research activities.

Establishment of the technical committees took place shortly after introduction of each piece of legislation and created two distinct levels: i) the technical committees for the technical and scientific decision making process and ii) the regulatory committees for the political decision making process. The latter was the meeting of the Competent Authorities (CA), composed of national representatives e.g. from the politically responsible ministries.

TABLE 1. Examples for Results of Integrating Science into EU Chemicals Legislation

document	characteristics
Technical Guidance Document (TGD) on Risk Assessment	guidance on exposure and effect assessment and risk characterization laying down the harmonized risk assessment method to be applied in the EU
EUSES	implementation of the risk assessment method described in the TGD in a software tool
IUCLID and New Chemicals Database (NCD)	databases to store information on substances according to harmonized templates
Manual of Decisions (*28*)	policy document laying down regulatory and technical decisions taken at the TC NES and endorsed by the CAs on the evaluation of new substances
Risk Assessment Reports	comprehensive risk assessments for priority substances based on the TGD
PBT Factsheets	comprehensive PBT assessments for prioritized substances

For example, at TC NES the risk assessments prepared by the RMS were discussed with all stakeholders, with the aim to reach consensus on the conclusions of the risk assessments based on science and on the appropriate guidance (phase 3 of the evaluation under ESR). The risk assessment results were forwarded to the CA meeting, where the need for risk reduction was discussed based on, where relevant, a risk reduction strategy (phase 4 of the evaluation under ESR). Initially, the technical committees were coordinated by the policy Directorates General and then by the European Chemicals Bureau (ECB), which was created in 1993 for this purpose (*27*).

Results and Examples. Some results relating to the integration of science into legislation on industrial chemicals are presented in Table 1 (all documents listed are available from http://ecb.jrc.ec.europa.eu).

The main scientific achievements are the Technical Guidance Document (TGD) and its supporting IT tool, the European Union System for the Evaluation of Substances (EUSES) (*29*). The EU legislation on new and existing substances laid down general principles for risk assessment but did not include details on how to actually carry out the different steps. Therefore the TGD was developed providing extensive supplementary technical details for conducting hazard identification, effect, and exposure assessment and risk characterization for human health and the environment. The TGD was revised several times to adapt to scientific progress within chemical risk assessment: in 1996 an amalgamated version of the separate guidances for new and existing substances was produced and in 2003 the experiences from performing risk assessments was integrated (*30*). The work was coordinated by the ECB, setting up 12 expert groups to draft guidance on exposure and effects assessment and with extensive stakeholder consultation. This process was continued during the preparation for REACH where, via the REACH Implementation Projects (RIPs), extensive REACH guidance was produced and later published by ECHA.

The complexity of the risk assessment methodology laid down in the TGD, especially on exposure estimation, necessitated the development of EUSES. Examples of more complex exposure estimation are the introduction of multimedia fate modeling for the assessment of risks on a regional scale and the development of Emission Scenario Documents (ESDs) for different industrial categories for the local scale. The ESDs were developed in close collaboration with the OECD Exposure Assessment Task Force.

The TGD harmonized the risk assessment methodology at EU level and was a state-of-the-art on chemical risk assessment covering human health and environment, starting from a screening step and ending with quantitative effect and exposure assessment (using either measured and/or modeled data) to be compared in a risk characterization. Examples of the integration of several complex scientific issues into accepted EU guidance is given in Examples 1, 2, and 3.

Example 1. From Assessment Factors to Statistical Extrapolation. Statistical extrapolation methods to derive environmental effects thresholds using Species Sensitivity Distributions were developed by Van Straalen and Denneman (1989) and Løkke (1994) (*31, 32*). In the TGD of 1996 this method was mentioned for the first time in an appendix. The main method to be applied was the use of assessment factors to derive the Predicted No-Effect Concentration (PNEC). Before the revision of the TGD in 2003, a scientific debate was ongoing about statistical extrapolation (*33, 34*). In 2001, on the initiative of the ECB, a workshop was organized examining under which conditions statistical extrapolation techniques might be used to derive PNECs. This led to the establishment of several criteria like minimum species requirements, sample size and distribution fitting. In the TGD of 2003 this technique is consequently incorporated as a supportive method. PNEC derivation with the method has taken place thereafter for metals like zinc, copper, and nickel.

Example 2. Environmental Risk Assessment of Metals: Introducing Bioavailability Concepts. In the TGD of 1996 a dedicated appendix was incorporated on "Environmental risk assessment for metal and metal compounds". Already then it was realized that "it is of utmost importance that both PEC and PNEC are based on similar levels of availability in both exposure and effect assessment, taking the speciation into account" (PEC is Predicted Environmental Concentration). However, methods to incorporate bioavailability were lacking. Research was already ongoing at that time on the development of the biotic ligand model (BLM) as a tool to evaluate quantitatively the manner in which water chemistry affects the speciation and biological availability of metals in aquatic systems (*35*). The prioritization and evaluation of several metals under ESR significantly enhanced the further development of these methods. Several research projects were started and workshops were organized, where the most significant was the Metals Environmental Risk Assessment Guidance (MERAG) project sponsored by the metals industry (*36, 37*). Concretely, methods incorporating bioavailability in metals risk assessment were used for zinc and zinc compounds (*38*). The latest examples are nickel and copper published through ESIS and the Web site of ECHA, respec-

TABLE 2. Key Aspects of Paradigm Shift under REACH

previous legislation	new legislation (REACH)
burden of proof on authorities	burden of proof on industry
risk assessment followed by risk management	safety assessment integrating risk management
management of risks often divided in human health and environment, respectively	focus on risk management triggers integrated management of health and environmental risks
sequential involvement of expertise	integrated involvement of multidisciplinary expertise
guessing uses and exposure in the chemical life cycle - little supply chain communication	increased supply chain communication leading to targeted use and exposure information
lack of knowledge on use and exposure leading to less informed generation of information on inherent properties and less focused assessments and management	increased knowledge on use and exposure leading to focused information generation, assessment and management addressing actual uses and exposure routes

tively. Through extensive consultations in the TC NES meetings, criteria were set for the application of BLMs, including application across species. This has led to a dedicated guidance document under REACH, laying down the agreed principles on how to incorporate bioavailability by applying BLMs (*39*).

Example 3. PBT Assessment: Screening Tools for B Assessment. In the TGD of 2003 a testing strategy is presented for the assessment of the Bioaccumulation (B) criterion of the PBT and vPvB assessment. This guidance was one of the results of the EU interim PBT strategy but was relatively limited. As measured data on bioaccumulation were often lacking, the development of screening methods was considered essential. Discussions in the PBT WG on the potential PBTs from the candidate list sparked further developments in this area. In order to develop more detailed guidance under REACH, the PBT Drafting Group was formed in 2005. It was chaired by the ECB and consisted of representatives from the Commission, Member States, industry associations, and NGOs and incorporated scientific developments and experience from the PBT WG. This has resulted in more elaborated guidance published by ECHA, based for example on an ECETOC project and research of Dimitrov et al. (2003) in the field of (Q)SAR (*40, 41*). In this guidance on B assessment there is a separate appendix on indicators for limited bioconcentration potential, for example molecular size, molecular weight, log Kow, and octanol solubility (*42*).

The REACH Paradigm Shift

An overview of the REACH paradigm shift is shown in Table 2.

From "Risk Assessment Followed by Management" to "Safety Assessment Integrating Risk Management" - Key Role of REACH Exposure Scenarios. Under the ESR legislation a multistep procedure was in place, see above, and especially transfer from phase 3 to 4 could cause problems: when risks were identified, these assessments were transferred to another group of risk management experts to formulate an appropriate risk reduction strategy. This was often associated with some difficulties as it was not always clear to the risk managers under which specific use conditions a risk was identified, thus making it difficult to identify and suggest the most appropriate and efficient risk management measures. The time involved in agreeing, finalizing, and transferring risk assessments to risk managers sometimes led to the situation that risk assessments or parts thereof could be outdated, causing difficulties in formulating the best possible proposal for risk management. Once a risk reduction strategy was agreed, it had to be implemented. This could be done by different means e.g. harmonized C&L, restriction that would set out specific conditions or a complete ban for specific uses, or it could be accomplished via a voluntary agreement with industry. Only then industry actually had to do the practical implementation. Thus, the process was sometimes cumbersome and slow, not always updated, and targeted to managing actual risks.

With REACH, the terminology underwent a change from *risk* to *safety*. Given the improved information, REACH safety assessments can be more targeted than previously (see also next paragraph) but otherwise follow the well-known elements of a traditional risk assessment. This will lead to a conclusion as to whether risks are controlled or not based on the current use of the substance (comparable to the risk assessment made by the authorities previously). If that first assessment (normally assessing 'current use') of the substance does not show that risks are controlled, the registrant has to do *iterations* either improving the data or methods used in the assessment or assuming stricter use conditions/risk management measures (RMM) that will reduce exposure and the associated risk(s) and continue until it can be shown that risks are controlled for all uses throughout the life cycle of that substance. When this is the case, the assessment is documented in the Chemical Safety Report, and the use conditions (Operational Conditions and RMMs) shown to lead to control of risks (i.e., those conditions assumed in the final iteration) should be communicated to the (downstream) users (DU) via so-called *exposure scenarios* (ES) attached to the Safety Data Sheets. The exposure scenarios are a crucial characteristic of REACH implementation and play a double role: 1. they are the *final output* informing the DU how to apply a substance in such a way that risks are controlled, and 2. they contain the *determinants/drivers of exposure* needed to *estimate the corresponding exposure* during the iterative safety assessment. The DU in turn simply has to implement the use conditions specified in the ESs communicated to him. If the ES does not address his use, the DU can either inform his supplier (asking the supplier to develop an ES for his use) or take over the responsibility of doing the Chemical Safety Assessment and develop ESs targeted to his use, or consider an alternative supplier.

Consequently, a key difference in REACH is that risk management is *integrated* in the assessment process (*safety* assessment) and directly communicated to the users as annexes to Safety Data Sheets, thus the information flow and implementation of risk management measures occur within industry. Authorities may check the registrations and assessments in the Evaluation phase of REACH and ask for further information and/or suggest restrictions if they consider that risks are not controlled.

From Guesstimates to Knowledge - Entire Life Cycle and Targeted Assessments. REACH ESs are the key tool for communicating and implementing RMMs. The concept of ESs also enables a more targeted assessment compared to the previous system. First, industry is directly responsible and holds specific (use) information, and, in particular, the involvement of the supply chain (see above) enables a much more detailed mapping of actual uses and use conditions, compared to the earlier situation. Targeting the assessment to actual/specified uses thus not only enables more precise exposure estimation but also enables a more informed advice on how to manage risk for concrete uses and use conditions, compared to the previous system where the authorities sometimes had to base their assessments and advice on guesstimates.

More specific chemical use information both improves the exposure estimation and risk management and is also used in generating information on inherent properties. The REACH standard information requirements as set out in REACH Annex VI to X can be adapted based on specific information on use, exposure routes, and exposure levels. Thus the Integrated Testing Strategies outlined in the REACH guidance on Information Requirements and Chemical Safety Assessment (*43*) also addresses how knowledge on use and exposure can influence information generation, including testing.

Integration of Assessment and Management of Health and Environmental Risks. Environmental release of and exposure to industrial chemical substances originates from manufacture and use, i.e. human activities so the same use/process may cause exposure of humans and the environment. An occupational use may lead to occupational exposure AND environmental release/exposure, and a consumer use may lead to consumer exposure AND environmental release/exposure. The ESs should not solve one problem and at the same time create another, and thus the operational conditions and RMM specified in a given ES should at the same time protect the worker (or consumer) AND the environment. This requires a closer cooperation between specialists working with occupational/consumer exposure and safety and those dealing with environmental release and exposure. *Overall, the REACH safety assessment process is a very integrated process requiring a multidisciplinary team,* including toxicologists, eco-toxicologists, occupational hygienists, risk managers responsible for the environment, sales and marketing practitioners (and corresponding experts by the downstream users to map out the life cycle), etc.

REACH Formalizing the Precautionary Principle

Debate on application of the precautionary principle led in 2000 the European Commission to develop and publish a 'Communication on the precautionary principle' to inform interested parties on how the European Commission applies or intends to apply the principle (*44*). In relation to chemicals policy this was followed up by the REACH regulation (*4*), whose Recital 9 states that "*The assessment of the four main legal instruments governing chemicals in the community...*" showed the need "*...to do more to protect human health and the environment in accordance with the precautionary principle*". This is also recognized in Article 1 of the REACH legal text "Aim and scope" which states: "*This Regulation is based on the principle that it is for manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment. Its provisions are underpinned by the precautionary principle*". Most profoundly, the precautionary principle is put into operation in Title VII Authorization, which is motivated in Recital 69 as follows "*To ensure a sufficiently high level of protection for human health....., and the environment, substances of very high concern should, in accordance with the precautionary principle, be subject to careful attention....*":

The authorization scheme in REACH focuses on Substances of Very High Concern (SVHC). The criteria for identifying a substance as SVHC are listed in Article 57:

1. Substances meeting the criteria for carcinogen, mutagen, or toxic for reproduction (CMR) category 1A or 1B in accordance with the CLP Regulation (EC) No 1272/2008;

2. Substances meeting the criteria for PBT or vPvB as set out in Annex XIII of REACH;

3. Substances giving rise to an equivalent level of concern, for example endocrine disrupters.

REACH specifies the aim of the Authorization procedure in Article 55: "*The aim of this Title is to ensure the good functioning of the internal market while assuring that the risks from substances of very high concern are properly controlled and that these substances are progressively replaced by suitable alternative substances or technologies where these are economically and technically feasible. To this end all manufacturers or importers and downstream users applying for authorizations shall analyze the availability of alternatives and consider their risks, and the technical and economic feasibility of substitution*".

In practice, once a substance is identified as SVHC and based on priority setting included in Annex XIV of REACH, industry has to cease its use within a sunset date or provide an application for Authorization for specific use(s) within an application deadline. Depending on the specific properties, the use(s) of the substance, and the information provided in an application dossier, the authorities will decide whether an Authorization can be granted or not.

CMR substances category 1A or 1B are subject to the authorization process due to the severity of the effects they may cause and as they (in particular C and M substances) may act via a nonthreshold mechanism. They will be prohibited by default in consumer products, and they are also within the scope of particular hazardous substances for which authorities can suggest harmonized classifications. Identification of this class of substances for which the precautionary principle shall apply can also be observed in other legal instruments in the EU. For example in the recently adopted Regulation on plant protection products (*45*) and the proposed Regulation on biocides (*46*), so-called exclusion criteria are incorporated for CMR substances category 1A and 1B: active substances used in plant protection or in biocidal products will, in principle, not be allowed on the market if they are classified as such. Specifically for use in workplaces, use of C and M substances should be avoided or if this is not possible exposure should be minimized (*47*).

The formal inclusion of PBT substances under the Authorization procedure builds upon the experience under ESR, and the criteria for identification of PBT and vPvB substances are now laid down in a dedicated Annex of REACH and thus these criteria have now a legal basis comparable to the C&L criteria.

Substances of equivalent level of concern, for example endocrine disrupters, will be identified for Authorization on a more case-by-case basis. There is not yet a concrete scope for this, although some limited guidance, in particular on endocrine disrupters can be found in the REACH Guidance for the preparation of an Annex XV dossier on the identification of SVHC (*48*). Special focus on endocrine disrupters is in line with the Community Strategy for Endocrine disrupters (*49*) and the subsequent 'Staff working documents' on implementation of this strategy (for details, see ref *50*).

Another example of implementation of the precautionary principle is specified in REACH Annex 1, section 0.5, specifying that a registrant shall: "*While waiting for results of further testing, he shall record in his Chemical Safety Report (...) the interim risk management measures he has put in*

place and those communicated to the downstream users intended to manage the risks being explored". Thus, active management of exposure must take place awaiting further information to assess the risks.

In conclusion, REACH builds on the precautionary principle, most concretely implemented via the Authorization procedure for SVHC with potent hazardous properties or for which it can be difficult or impossible to establish thresholds (like for some CMRs) or where current methodologies and science do not allow the risks to be properly assessed (e.g. for PBTs). Thus, the introduction of the precautionary principle for such specific types of substances complements the safety/risk management outlined in the above section on the REACH paradigm shift.

Past Successes Carried Forward and Enhanced under REACH

The new REACH management principles outlined above address some of the main shortcomings of the previous legislation. At the same time REACH has taken over and further enhanced many of the successes of the past, already outlined. The following will give a brief overview of how REACH is building on these and how they have been maintained and/or enhanced.

The Best of the Past into One Legal Context. REACH replaced about 40 pieces of legislation, including many *directives* requiring implementation into all Member States' national legislation, into one *regulation* that is binding in its entirety and directly applicable in all Member States. REACH took the best from the previous legal texts. For example, the restrictions part of REACH is a continuation of earlier legislation, although it is used as a 'safety net' to be applied only if risks cannot be controlled by other procedures of REACH. The establishment of ECHA with its committee structure built on the experiences gained in the work of the ECB and its technical meetings. Also the principle of priority setting has continued and was built into REACH, e.g. via tonnage dependent registration and information requirements and via focus on SVHC. REACH has formalized priority setting in several activities from compliance check to authorization.

The REACH legal context also covers the new Regulations on Classification, Labeling and Packaging (*9*) and Test Methods (*15*). Both were for practical reasons put forward as separate legal texts; however, they are closely interlinked with REACH. Regarding C&L, previous harmonized classifications have been taken forward as has the principle that authorities can suggest harmonized classification (although limited to the most hazardous substances). The link to other international efforts has been assured via harmonization with the GHS (*10*). As a new element, industry will be asked to report self-classifications, which can be consulted in the classification and labeling inventory. The Test Methods Regulation builds significantly on past experiences and will be regularly updated to align with the latest validated test methods and with a close link to international developments within OECD.

REACH has also formalized some issues and activities, which were previously performed ad hoc. The technical meetings have been formalized via the ECHA committees, as has the PBT work through the inclusion of the criteria into REACH and through the Authorization procedure. Finally, it should be mentioned that REACH Annex I outlines and formalizes the general provisions for assessing substances and preparing the chemical safety report, building on the previous guidance on risk assessment (*30*).

Guidance and Tools. As most of the basic risk assessment principles remained the same under REACH, the TGD was taken forward as the starting point in the new guidance on Information Requirements and Chemical Safety Assessment (*43*), while also elaborating new guidance reflecting how the paradigm shift described above should be implemented, including e.g. Integrated Testing Strategies and development of Exposures Scenarios for managing risks. To harmonize the processes and methods under REACH, guidance development via the RIPs was initiated in parallel with the REACH negotiations, adopting an approach that involved all interested stakeholders facilitated by the ECB.

Of key importance for the registration process is the IUCLID 5 software (*51*) to be used for creating the dossier that will constitute the registration. Development of IUCLID 5 was a huge project lead by ECB and was, inter alia, built on the experience obtained with the previous versions of IUCLID and the New Chemicals Database. In parallel to this, another significant task was the development, in close cooperation between ECB and OECD, of the OECD harmonized templates for reporting information on inherent properties. IUCLID 5 implements these templates, making IUCLID 5 a database for storing data on chemicals in an internationally compatible format, usable for regulatory requirements in other jurisdictions.

International Perspective. In the REACH drafting and negotiation process significant emphasis was placed on making the regulation compatible with World Trade Organization (WTO) rules and requirements. Likewise, it was key to make REACH nondiscriminatory and thus it applies equally to substances manufactured within and substances imported into the EU. Beside these issues directly related to international trade, emphasis was put on harmonization of legislation (e.g., CLP regulation harmonized with GHS and test methods with OECD progress), guidance (harmonizing with international principles of assessing risks), and tools (OECD harmonized templates implemented in IUCLID making it a global tool). Overall, the efforts of harmonizing with international progress have thus been largely enhanced with REACH.

Stakeholder Dialogue. The basic principle of having stakeholders participating directly or as observers to meetings at all levels was a crucial contribution to the ultimate enactment of REACH and has been maintained by ECHA and by the REACH and CLP competent authorities meeting. Under REACH, stakeholders were and are also more formally involved in the guidance development process in the past via the RIPs (see above) and now via ECHA's Partner Expert Groups (see ref *52* for details). Finally, the development of the REACH regulation itself was subject to heavy stakeholder interaction, including the process leading up to the White Paper (*53*) and the public Internet consultation on a draft REACH text in 2003 (see e.g. ref *54* for details).

Discussion - How Scientific-Technical Support Informed the Development and Implementation of REACH

The knowledge base on chemicals has increased substantially since the start of the EU chemicals legislation, especially for information on intrinsic properties, use, and exposure. While the C&L of substances within the Dangerous Substances Directive was based on existing information collected by authorities, the legislation on new and existing substances aimed at risk assessment based on a defined data set submitted by industry. Thus, the main regulatory achievements of the previous chemicals legislation were the harmonized classifications, the evaluation of all new substances and the existing priority substances, and the PBT assessments for prioritized existing substances. The number of existing substances evaluated may appear small compared to the total on the market; however, these were prioritized substances with a high expectation of regulatory outcome (*7*). Now, REACH requires registration dossiers for all substances

above 1 tonne per year per manufacturer or importer. The overall trend has been towards a systematic evaluation of all chemicals placed on the EU market within a defined time scale.

The main achievement regarding incorporation of science in the previous chemicals legislation was the TGD on risk assessment, establishing the EU harmonized risk assessment method in a transparent way, thus preventing certain dangerous substances from entering or staying on the EU market (*7*). The risk assessment methods have evolved substantially since their introduction. With respect to effects assessment the development has been from straightforward testing regimes based on tonnage triggers to integrated testing strategies involving a weight of evidence approach based on all data available including results from nonanimal test methods. More testing methods became available for more end points and species. Refined methods were developed for the derivation of no-effect levels. A whole set of exposure estimation models and tools, from release estimation on a local scale based on emission factors to complex multimedia fate models, became available. All aspects of complexity have increased since the start of EU chemicals legislation requiring development of tools like EUSES. REACH continues the scientifically driven guidance and tools development with increased focus on safety and management.

Platforms like the ECB (and now ECHA) created(s) opportunities for scientific development. Stakeholders, often with a close connection to the scientific community on chemical risk assessment, could channel results of research projects to these platforms. This led to a spin-off from the chemicals legislation framework to scientific development in two directions. First, the discussions on the risk assessments of the individual substances often led to the identification of unresolved scientific issues which initiated new research projects. Second, also new scientific developments found their way to the decision making process. The latter was especially true for the guidance development during the revisions of the TGD. In addition, the implementation of guidance often led to a reopening but also deepening of the scientific debate on a certain aspect, contributing to further scientific developments. Also under REACH new science developments will be addressed where industry has the opportunity to introduce these in their Chemical Safety Assessments. That will undoubtedly trigger discussions on regulatory acceptance and therefore lead to potential inclusion of new scientific developments in the ECHA guidance documents.

The regulatory processes and guidance to implement the regulation or to meet its obligations are becoming more and more complex. With respect to chemicals risk assessment future developments may include for example i) cumulative and multiroute exposure, ii) mixture toxicity, iii) probabilistic risk assessment, and iv) redefining PBT criteria (*55*). This increasing complexity and additional scientific developments, in combination with better transparency, impacts the implementation and workability of the EU chemicals legislation. Also integration is an obvious trend, from hazard to risk, integrating effects and exposure, and from risk to safety, integrating risk and risk management, but also the integration of environment and human health risk assessment, e.g. in the concept of indirect human exposure via the environment.

The issue of chemical safety is global, and international organizations are critical players in this area, for example the OECD on testing methods, Emission Scenario Documents and the HPVC program, the United Nations on C&L, and the World Health Organization with its International Programme on Chemical Safety dealing with methodological aspects. As a consequence there is a continuous exchange between geographical regions on their chemical management programs including the risk assessment methodologies. An example of this is PBT assessment where the OECD and US EPA have developed screening tools (*56*).

REACH combines the successes of the past and the need for new management principles shifting responsibility for chemical safety to industry with a strong focus on risk management and formal introduction of the precautionary principle. The process of developing and implementing REACH is taking place in an open dialogue with all interested stakeholders and adapting to international progress.

Furthermore, the REACH regulation and its implementation will be regularly reviewed and updated as needed. This enables an adaptation to experiences from its implementation as well as to developments in science or technology.

Currently, the new forms of substances introduced by nanotechnology are discussed, both in relation to the possible need for adapting REACH and to ensure that the supporting guidance appropriately addresses the properties and potential risks of nanomaterials. The REACH competent authorities have established a subgroup to specifically look at implementation issues related to nanomaterials. Further, the Commission's Joint Research Centre has been asked to assist with providing advice on how the guidance for identification and naming of substances in REACH (*57*) and on Information Requirements and Chemical Safety Assessment (*43*) could be updated to better reflect the specific properties of nanomaterials.

Thus, although REACH is a significant step forward in relation to managing risks of chemical substances, the travel continues and experience and scientific and technological development will trigger future adaptations of legislation and guidance.

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Supporting Information Available

A list of the abbreviations used in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited

(1) Council Directive 67/548/EEC of 16 August 1967 on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. OJ L96.

(2) Commission Regulation 1488/94 (EC) of 28 June 1994 laying down the principles for the assessment of risks to man and the environment of existing substances in accordance with Council Regulation 793/93 (EC). OJ L161.

(3) Commission Directive 93/67/EEC of 20 July 1993 laying down the principles for assessment of risks to man and the environment of substances notified in accordance with Council Directive 67/548/EEC. OJ L227/9.

(4) Corrigendum to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396, 30.12.2006). OJ L136, 29.5.2007.

(5) Bodar, C. W. M.; Berthault, F.; De Bruijn, J. H. M.; Van Leeuwen, C. J.; Pronk, M. E. J.; Vermeire, T. G. Evaluation of EU risk assessments existing chemicals (EC Regulation 793/93). *Chemosphere* **2003**, *53*, 1039–1047.

(6) Gebel, T.; Lechtenberg-Auffahrt, E.; Guhe, C. About hazard and risk assessment:Regulatory approaches in assessing safety in the European Union chemicals legislation. *Reprod. Toxicol.* **2009**, *28*, 188–195.

(7) Van Leeuwen, C. J.; et al. The management of industrial chemicals in the European Union (REACH). In *Risk Assessment of Chemicals. An Introduction*; Van Leeuwen, C. J., Vermeire, T. G., Eds; Springer Publishers: Dordrecht, The Netherlands, 2007; p 511.
(8) Council Directive 88/379/EEC of 7 June 1988 on the approximation of laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations. OJ L187.
(9) Regulation (EC) No.1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directive 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No. 1907/2006. OJ L353.
(10) *Globally Harmonized System of Classification and Labelling of Chemicals*; United Nations, New York, Geneva, 2005; ISBN 92-1-216463−3.
(11) Council Directive 79/831/ EEC amending for the 6th time Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packing and labelling of dangerous substances. OJ L259.
(12) Council Directive 92/32/EEC of 30 April 1992 amending for the 7th 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 L154.
(13) Baraibar Fontanes, J.; Olsson, H.; Sokull-Kluettgen, B. *European List of Notified Chemical Substances ELINCS*. EUR 23923 EN; JRC-IHCP: Luxembourg, 2009.
(14) Ex-ECB New Chemicals Web site. http://ecb.jrc.ec.europa.eu/new-chemicals (accessed September 22, 2010).
(15) Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). OJ L142.
(16) Council Regulation 793/93/EEC of 23 March 1993 on the evaluation and control of the risks of existing substances. OJ L084.
(17) European Inventory of Existing Commercial Chemical Substances of 15 June 1990. OJ C/146A. Corrigendum published in OJ C54, 2002.
(18) Decision-Recommendation of the Council on the Systematic Investigation of Existing Chemicals. Organisation for Economic Co-operation and Development (OECD), 1987. OECD Publications, C(87)90 (Final).
(19) United Nations. 1992. Rio Declaration, Agenda 21. United Nations Conference on Environment and Development (UNCED), Rio de Janeiro, Brazil.
(20) European chemical Substances Information System (ESIS) Web site. http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=dat (accessed September 22, 2010).
(21) Hansen, B. G.; Van Haelst, A.; Van Leeuwen, K.; Van der Zandt, P. Priority setting for existing chemicals: European union risk ranking method. *Environ. Toxicol. Chem.* **1999**, *18* (4), 772–779.
(22) Munn, S. J.; Hansen, B. G. EU risk assessment: science and policy. *Toxicology* **2002**, *181−182*, 281–285.
(23) Council Directive 76/769/EEC of 27 July 1976 on the approximation of the laws, regulations and administrative provisions of Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations. OJ L262.
(24) An interim strategy for management of PBT and vPvB substances. Doc.ENV/D/432048/01, NOTIF/36/2001.
(25) Identification of potential PBTs or vPvBs among the IUCLID high production volume chemicals. Doc. ECB 4/14/02. REV1.
(26) Ershow, A. G. Research science, regulatory science, and nutrient databases: achieving an optimal convergence. Capstone Lecture. *J. Food Compos. Anal.* **2003**, *16*, 255–268.
(27) Communication to the Council and the European Parliament establishing the European Chemicals Bureau. Notice no. 93/C1/02. OJ C001.
(28) Manual of decisions for implementation of the sixth and seventh amendments to Directive 67/548/EEC on dangerous substances (Directives 79/831/EEC and 92/32/EEC). EUR 22311 EN; JRC-IHCP; Luxembourg, 2006.
(29) EUSES, the European Union System for the Evaluation of Substances. European Chemicals Bureau (ECB) and National Institute of Public Health and the Environment (RIVM). Available from: http://ecb.jrc.ec.europa.eu/euses/ (accessed September 22, 2010).
(30) Technical Guidance Document on risk assessment in support of Commission Directive 93/67/EEC on risk assessment for new notified substances, Commission Regulation (EC) No. 27 1488/94 on risk assessment for existing substances, and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. EUR 20418 EN; JRC-IHCP, Luxembourg, 2003.
(31) Van Straalen, N. M.; Denneman, C. A. J. Ecotoxicological evaluation of soil quality criteria. *Ecotox. Environ. Saf.* **1989**, *18*, 241–251.
(32) Løkke, H. Ecotoxicological extrapolation: tool or toy? In *Ecotoxicology of soil organisms*; Donkers, M. H., Eijsackers, H., Heimbach, H., Eds.; SETAC Publication Series, Lewis Publishers: 1994.
(33) Forbes, T. L.; Forbes, V. E. A critique of the use of distribution-base extrapolation models in ecotoxicology. *Funct. Ecol.* **1993**, *7*, 249–254.
(34) Newman, C. M.; Ownby, D. R.; Mezin, C. A.; Powell, D. C.; Christensen, T. R. L.; Lerberg, S. B.; Andersson, B. A. Applying species-sensitivity distributions in ecological risk assessment: assumptions of distribution type and sufficient number of species. *Environ. Toxicol. Chem.* **2000**, *19*, 508–515.
(35) Paquin, P. R.; Farley, K.; Santore, R. C.; Kavvadas, C. D.; Mooney, K. G.; Winfield, R. P.; Wu, K.-B.; Di Toro, D. M. *Metals in Aquatic Systems: A Review of Exposure, Bioaccumulation, and Toxicity Models*; SETAC: Pensacola, USA, 2003.
(36) *Bioavailability of Metals in Terrestrial Ecosystems: Importance ofPartitioning for Bioavailability to Invertebrates, Microbes, and Plants*; Allen, H. E., Ed.; SETAC: Pensacola, USA, 2001.
(37) MERAG: Metals Environmental Risk Assessment Guidance. The International Council on Mining and Metals (ICMM); London, UK, 2007.
(38) Bodar, W. M.; Pronk, M. E. J.; Sijm, T. H. M. The European Union Risk Assessment on Zinc and Zinc Compounds: The Process and the Facts. *Integr. Environ. Assess. Manage.* **2005**, *1*, 301–319.
(39) Guidance on information requirements and chemical safety assessment. Appendix R.7.13-2: Environmental risk assessment for metals and metal compounds; ECHA: Helsinki, July 2008.
(40) *Alternative Testing Approaches in Environmental Safety Assessment. Technical Report 97*; ECETOC: Brussels, Belgium, 2005.
(41) Dimitrov, S. D.; Dimitrova, N. C.; Walker, J. D.; Veith, G. D.; Mekenyan, O. G. Bioconcentration potential predictions based on molecular attributes - an early warning approach for chemicals found in humans, fish and wildlife. *QSAR Comb. Sci.* **2003**, *22*, 58–68.
(42) Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT Assessment. ECHA; May 2008.
(43) Guidance on information requirements and chemical safety assessment. ECHA; May 2008.
(44) Communication from the Commission on the precautionary principle; COM(2000) 1 final; European Commission: Brussels, 2000.
(45) Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L309.
(46) Proposal for a Regulation of the European Parliament and of the Council concerning the placing on the market and use of biocidal products. {SEC(2009) 773} {SEC(2009) 774} /* COM/2009/0267 final - COD 2009/0076 */. 2009.
(47) Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC) of 29 4 2004. OJ L158.
(48) Guidance for the preparations of an Annex XV dossier on the identification substances of very high concern. ECHA; June 2007.
(49) Communication from the Commission to the Council and the European Parliament - Community Strategy for Endocrine Disrupters; COM(1999) 706 final; European Commission: Brussels, 1999.
(50) European Commission Endocrine Disrupters Web site. http://ec.europa.eu/environment/endocrine/documents/index_en.htm (accessed September 22, 2010).
(51) ECHA's IUCLID5 Web site. http://iuclid.echa.europa.eu/ (accessed September 22, 2010).
(52) ECHA's Consultation procedure on guidance. Available at http://echa.europa.eu/doc/ECHADocuments/ConsultationProcedure-OnGuidance.pdf (accessed September 22, 2010).
(53) White Paper - Strategy for a future Chemicals Policy /* COM/2001/0088 final */. European Commission: Brussels, 2001.

(54) REACH history Web sites. http://ec.europa.eu/enterprise/sectors/chemicals/documents/reach/archives/white-paper/index_en.htm (accessed September 22, 2010) and http://ec.europa.eu/environment/chemicals/reach/background/index_en.htm (accessed September 22, 2010).
(55) Arnot, J. A.; Mackay, D. Policies for chemical hazard and risk priority setting: can persistence, bioaccumulation, toxicity, and quantity information be combined. *Environ. Sci. Technol.* **2008**, *42*, 4648–4654.
(56) Gouin, T. The precautionary principle and environmental persistence: prioritizing the decision-making process. *Environ. Sci. Policy* **2010**, *13*, 175–184.
(57) Guidance on identification and naming of substances under REACH. ECHA; June 2007.

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