Integrated Environmental Assessment and Management — Volume 6, Number 3—pp. 325–337
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Potential Application of Ecological Models in the European Environmental Risk Assessment of Chemicals I: Review of Protection Goals in EU Directives and Regulations

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(Submitted 13 October 2009; Returned for Revision 3 February 2010; Accepted 19 February 2010)

ABSTRACT

Several European directives and regulations address the environmental risk assessment of chemicals. We used the protection of freshwater ecosystems against plant protection products, biocidal products, human and veterinary pharmaceuticals, and other chemicals and priority substances under the Water Framework Directive as examples to explore the potential of ecological effect models for a refined risk assessment. Our analysis of the directives, regulations, and related guidance documents lead us to distinguish the following 5 areas for the application of ecological models in chemical risk assessment: 1) Extrapolation of organism-level effects to the population level: The protection goals are formulated in general terms, e.g., avoiding ''unacceptable effects'' or ''adverse impact'' on the environment or the ''viability of exposed species.'' In contrast, most of the standard ecotoxicological tests provide data only on organism-level endpoints and are thus not directly linked to the protection goals which focus on populations and communities. 2) Extrapolation of effects between different exposure profiles: Especially for plant protection products, exposure profiles can be very variable and impossible to cover in toxicological tests. 3) Extrapolation of recovery processes: As a consequence of the often short-term exposures to plant protection products, the risk assessment is based on the community recovery principle. On the other hand, assessments under the other directives assume a more or less constant exposure and are based on the ecosystem threshold principle. 4) Analysis and prediction of indirect effects: Because effects on 1 or a few taxa might have consequences on other taxa that are not directly affected by the chemical, such indirect effects on communities have to be considered. 5) Prediction of bioaccumulation within food chains: All directives take the possibility of bioaccumulation, and thus secondary poisoning within the food chain, into account. Integr Environ Assess Manag 2010;6:325–337. © 2010 SETAC

Keywords: Chemical risk assessment, Protection goals, Data requirements, Ecological models

Critical Review

INTRODUCTION

In the European Union (EU), chemicals are assessed under different regulatory frameworks with respect to their risks on humans and the environment. The directives or regulations relate to the uses of the chemicals, e.g., plant protection products, biocides, pharmaceuticals, or industrial chemicals. In addition, substances are also evaluated to set Environmental Quality Standards (EQS) for the protection of environmental compartments, e.g., surface waters. The European legislation can be supplemented by national laws, as is the case for plant protection products, where the active substances have to be evaluated at the EU level but the products must be registered at the national level.

The objective of this review is to compare the environmental protection goals in the different EU directives and to explore their consequences for the potential use of ecological models in the risk assessment of chemicals. This study is the first of a series of 2. It extracts the protection goals from the different directives and supporting documents, as well as the data requirements for the aquatic environment and the approaches used for risk characterization. The second study presents a review of models and assesses whether they can address the protection aims (Galic et al. this issue). We focus mainly on the aquatic environment (freshwater) because this is the most extensively considered environmental compartment in all the directives which are to be analyzed here. However, other environmental compartments are discussed as well, whenever they are explicitly considered in these directives.

We compared the following EU directives and regulations that include risk assessment for chemicals: Directive 91/414/EEC on plant protection products (EC 1991, using the consolidated text including amendments from EC 2004a) replaced now by the regulation concerning the placing of plant protection products on the market (EC 2009a), Directive 98/8/EC on biocidal products (EC 1998), replaced by regulation COM(2009)267 (EC 2009b), Directive 2004/27/EC on medicinal products for human use (EC 2004b), 2004/28/EC on veterinary medicinal products (EC 2004c), Regulation 1907/2006 on chemicals (EC 2007a), and

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Published online 3 March 2010 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ieam.69

Directive 2000/60/EC (Water Framework Directive, WFD, EC 2000a). Detergents as regulated under Regulations 648/2004 and 907/2006 (EC 2004d, 2006) were not considered any further here, because their environmental assessment is focused on biodegradability. Although a complementary risk assessment is required for those surfactants failing ultimate biodegradability tests, this assessment is based on acute tests for algae, *Daphnia*, and fish as covered by other directives and guidance documents (e.g., EC 2003). Directive 2001/79/EC (EC 2001) was not analyzed either, because the assessment of additives in animal nutrition (feed additives) is based on principles equivalent to those for veterinary medicines (SANCO 2003). The Marine Strategy Framework Directive (2008/56/EC, EC 2008a) was not explicitly considered because its aim (to achieve a ''good environmental status'') and approaches are in line with those of the Water Framework Directive 2000/60/EC (EC 2000a); for synthetic compounds, for example, it directly refers to the priority substances under Directive 2000/60/EC. Other directives relating to the protection of the environment, such as the Habitat Directive (92/43/EEC, EC 2007b), do not include risk assessment of chemicals.

The EU has adopted the Precautionary Principle, whereby if the uncertainty of a risk is too large, precautionary action should be taken until the uncertainties can be reduced. However, this is a general principle for handling risks, which does not specify the protection goals. Protection goals can be set at different levels of biological organization using different levels of protection. For humans, the protection goal is set at the individual level, with the aim of protecting all humans against harm, while for the environment, various protection goals are possible in principle. Brock et al. (2006) argued that different protection principles can be appropriate for different ecosystems in a landscape, e.g., for drainage ditches in agricultural areas as compared to water bodies in or connected to nature protection areas. However, the authors point out that questioning the appropriateness of principles is a question for society, while defining criteria for the different principles falls within the scientific domain. Brock et al. (2006) suggest a set of 4 protection principles leading to different levels of protection: 1) Pollution prevention principle: This principle generally aims to avoid any pollution of an ecosystem. 2) Ecological threshold principle: This principle assumes that ecosystems can tolerate a certain degree of stress without adverse effects to their structure and function. 3) Community recovery principle: Based on the observation that the abundance and structure of natural populations vary in space and time, this principle assumes that reductions in population abundance are tolerable as long as they are within the natural range of variability, and the recovery of the population is likely. 4) Functional redundancy principle: A decrease in biodiversity might be tolerated for some situations or ecosystems, as long as the ecological function is maintained.

In the sections to follow, the EU directives are compared based on their associated protection principles and the data and approaches they use to meet their protection goals.

PROTECTION GOALS

Plant protection products

Plant protection products are regulated under Directive 91/414/EEC and are defined as active substances or preparations intended to ''protect plants or plant products against all harmful organisms or prevent the action of such organisms ...., influence the life processes of plants, other than as a nutrient..., preserve plant products..., destroy undesired plants, or destroy parts of plants, check or prevent undesired growth of plants'' (EC 2004a). Compared with other classes of substances, plant protection products (and some uses of biocides) are thus unique, because they have to be biologically active and they are intentionally released into the open environment.

With respect to environmental protection, Directive 91/414/EEC states that ''member states shall ensure that the use of plant protection products does not have any long-term repercussions for the abundance and diversity of nontarget species'' (EC 2004a). This has 2 important consequences for risk assessment: the protection of populations and communities (not individual organisms), and the possibility of accepting some short-term effects if followed by recovery. In the following, we focus on the protection of freshwater ecosystems. Saltwater organisms are not considered under 91/414/EEC because protecting the ''edge-of-field water bodies'' that are adjacent to agricultural areas excludes relevant exposure of marine ecosystems. In view of the possible exposure, the risk of plant protection products has to be assessed for soil organisms, honey bees, and other nontarget arthropods, as well as birds and mammals.

With respect to freshwater organisms, the protection goal is described in Annex VI (the Uniform Principles) of Directive 91/414/EEC as: ''[...] no authorization should be granted if the toxicity/exposure ratio for fish and *Daphnia* is less than 100 for acute exposure and less than 10 for long-term exposure [...] unless it is clearly established through an appropriate risk assessment that under field conditions no unacceptable impact on the viability of exposed species [...] occurs.'' Thus, the critical point is to define what has to be considered an unacceptable impact. The Guidance Document on Aquatic Ecotoxicology in the context of Directive 91/414/EEC (SANCO 2002) suggests the following list of unacceptable effects for consideration: 1) Decrease in biodiversity (overall species richness and densities, population densities of ecological key species and population densities of indicator species). 2) Impact on ecosystem functioning and functionality (water quality parameters, e.g., increase in toxic algae, depletion of oxygen, and decrease in harvestable resources such as fish). 3) Decrease in perceived aesthetic value or appearance of the water body (disappearance of species with a popular appeal [e.g., dragonflies or water lilies], visual mortality of individuals of fish, frogs, water fowl and other vertebrates, and symptoms of eutrophication, e.g., algal blooms).

No acceptable values are given, e.g., a decrease in population abundance; instead, recovery from short-term effects and thus absence of long-term effects is used as a decision criterion. For practical reasons, recovery within 8 weeks after application is often considered to be acceptable for populations assessed in microcosm or mesocosm studies, as suggested in the guidance documents on aquatic ecotoxicology (SANCO 2002). However, this criterion should be applied in a flexible way, considering aspects like the life cycle and recolonization potential of the affected species, as well as the magnitude and duration of indirect effects.

Thus, the risk assessment of the plant protection products is based on the Community Recovery Principle, which

accepts short-term effects and protects against long-term effects, on populations and communities. For some species, however, particularly vertebrates, mortality of individuals might also be an unacceptable effect, even if this mortality is not of significance on the population level. On the other hand, it has been proposed that in some cases (e.g., application in rice paddies or aquatic weed control uses) unacceptable impacts on ecological function instead of biodiversity parameters should be considered in the risk assessment (SANCO 2002).

On 21 October 2009, the European Council adopted the new regulation of the European Parliament and of the Council concerning the placing of plant protection products on the market repealing Council Directives 79/117/EEC and 91/414/EEC (EC 2009a). Within this regulation, the environmental protection goals have been slightly modified as compared to Directive 91/414/EEC, whereby long-range environmental transport, behavior of nontarget species, and biodiversity are explicitly mentioned.[1] However, the Uniform Principles (Annex VI of the Directive 91/414/EEC) defining the data requirements and decision criteria have not been refined yet. Thus, so far, it is not clear how, for example, the impact on behavior of species or on biodiversity should be assessed.

Biocidal products

Biocidal products are regulated under Directive 98/8/EC and are defined (article 2) as ''active substances and preparations containing 1 or more active substances, put up in the form in which they are supplied to the user, intended to destroy, deter, render harmless, prevent the action of, or otherwise exert a controlling effect on any harmful organism by chemical or biological means'' (EC 1998). The directive covers 23 product types, including disinfectants, preservatives, antifouling agents, and products used in pest control. With respect to the protection of the environment or nontarget organisms, the directive only mentions avoiding unacceptable effects (''no unacceptable effect... on the environment having particular regard to contamination of surface waters (including estuarine and seawater), groundwater and drinking water, (and) its impact on nontarget organisms''). The environmental protection goal of the biocide directive is not restricted to the aquatic compartment. This directive also considers ''any adverse effects arising in any of the 3 environmental compartments—air, soil, and water (including sediment)—and of the biota following the use of the biocidal product'' (EC 1998). Effects are, therefore, assessed for the aquatic (freshwater) compartment, microorganisms in sewage treatment plants, sediment organisms, soil organisms, the air compartment, secondary poisoning, and the marine aquatic and sediment compartment. What has to be considered an unacceptable effect on nontarget organisms is specified in Annex VI, which also gives the option of higher-tier tests to refine the risk assessment (similar to that for plant protection products)[2].

Thus, the protection goal refers to the viability of aquatic organisms, explicitly including estuarine and marine organisms because of the broader use patterns of biocides as compared to plant protection products. Directive 91/414/EEC uses the term ''viability of exposed species'' and Directive 98/8/EC uses ''viability of exposed organisms''; however, in practice, the focus is on ecosystem structure and function following the ecological threshold principle. The risk assessment for biocidal active substances is conducted according to the Technical Guidance Document for risk assessment of new and existing substances and biocides (TGD, EC 2003). In this document, it is argued that by extrapolating from the most sensitive test species to the theoretically most sensitive species in the field, ecosystem structure and, consequently, ecosystem function are protected[3]. In contrast to plant protection products, where entries into surface water bodies often result in a short-term exposure, the TGD focuses on long-term exposure situations. Thus, recovery of affected species is not an issue in the evaluation of effects, and therefore, risk assessment is based on the ecosystem threshold principle.

According to the proposal of a new regulation to replace Directive 98/8/EC, the fate and distribution of a biocidal product in the environment, as well as the contamination of surface waters, groundwater, drinking water, air, and soil, have to be considered, in addition to the impact on nontarget organisms, biodiversity, and the ecosystem, for the assessment of unacceptable effects on the environment (EC 2009b).

Human and veterinary medicinal products

Medicinal products are regulated under Regulation 726/2004 (EC 2004e) and the 2 Directives, 2004/27/EC (EC 2004b) for medical products for human use and 2004/28/EC (EC 2004c) for veterinary products. In the following, both directives are discussed together, highlighting their differences.

In contrast to plant protection and biocidal products, environmental risk assessment is not required for all medicinal products; no assessment is required for vitamins, electrolytes,

[1]According to article 4 of the new regulation (EC 2009a) ''a plant protection product ... shall have no unacceptable effects on the environment, having particular regard to the following considerations where the scientific methods accepted by the Authority to assess such effects are available: (i) its fate and distribution in the environment, particularly contamination of surface waters, including estuarine and coastal waters, groundwater, air and soil taking into account locations distant from its use following long-range environmental transportation; (ii) its impact on non-target species, including on the ongoing behaviour of those species; (iii) its impact on biodiversity and the ecosystem.''

[2]''The Member State shall not authorize a biocidal product where there is a reasonably foreseeable possibility of aquatic organisms including marine and estuarine organisms being exposed to the biocidal product if for any active substance or substance of concern in it: the PEC/PNEC is above 1 unless it is clearly established in the risk assessment that under field conditions the viability of aquatic organisms including marine and estuarine organisms is not threatened by the biocidal product according to the proposed conditions of use, or the bioconcentration factor (BCF) is greater than 1 000 for substances which are readily biodegradable or greater than 100 for those which are not readily biodegradable unless it is clearly established in the risk assessment that under field conditions no unacceptable impact, either directly or indirectly, occurs on the viability of exposed organisms including marine and estuarine organisms after use of the biocidal product according to the proposed conditions of use'' (EC 1998).

[3]''Certain assumptions are made concerning the aquatic environment which allow, however uncertain, an extrapolation to be made from single-species short-term toxicity data to ecosystem effects. It is assumed that ecosystem sensitivity depends on the most sensitive species, and protecting ecosystem structure protects community function. These two assumptions have important consequences. By establishing which species is the most sensitive to the toxic effects of a chemical in the laboratory, extrapolation can subsequently be based on the data from that species. Furthermore, the functioning of any ecosystem in which that species exists is protected provided the structure is not sufficiently distorted as to cause an imbalance. It is generally accepted that protection of the most sensitive species should protect structure, and hence function'' (EC 2003).

amino acids, peptides, proteins, carbohydrates, and lipids, in view of their rapid metabolism, degradation in the environment, or high effect thresholds. However, even if an environmental risk assessment has to be conducted, it would have no consequences on the authorization of a medicinal product *for human use*.[4] New veterinary products are only authorized with additional requirements to limit their environmental risks, e.g., distance measures to surface water bodies are used for pastures with treated animals.[5]

Human medicinal products enter the environment mainly by means of sewage treatment plants, resulting in a more or less constant exposure of the water bodies receiving the effluents. If a substance is characterized by a high adsorption potential to organic matter ($<I<K_{OC}>10\,000$ L/kg) and is not readily biodegradable, a risk assessment for the soil compartment is also required, which might include the assessment of effects on micro- and macroorganisms, including earthworms and plants.

The purpose of the study of the ecotoxicity of a veterinary medicinal product is to assess the potential harmful effects which the use of the product may have on the environment, and to identify any precautionary measures which may be necessary to reduce such risks. For veterinary products, the soil is usually the primary compartment where the substances enter the environment, e.g., by means of manure application to soil. Thus, the terrestrial effect assessment focuses on microbial function, earthworms, and plants. An issue specifically relating to veterinary products is that of organisms living in dung (dung beetles, dung fly larvae) being exposed to endo- or ectoparasiticides used in pasture treatments. However, ''exposure of the aquatic environment should consider run off and leaching of active ingredient to surface waters and groundwater as well as other routes of exposure of the aquatic environment, such as cattle entering water to drink and sheep crossing water after treatment. For fish farms, there will be a direct exposure of the aquatic environment to medicinal products'' (EMEA 2007). Thus, veterinary products might cause short-term and long-term aquatic exposure situations. In view of the potential use of products in marine aquaculture, an assessment of effects on marine organisms is necessary.

Industrial chemicals

Since 2007, industrial chemicals in the EU are regulated under the regulation concerning the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH, EC 2007a). A high protection level by avoiding adverse effects on the environment is mentioned in Article 1 (EC 2007a) as one of the general aims of REACH. Therefore, ''the environmental hazard assessment shall consider the following; (1) aquatic (including sediment), (2) terrestrial and (3) atmospheric compartments, and the potential effects that may occur (4) by means of food-chain accumulation and on the (5) microbiological activity of sewage treatment systems.'' (EC 2007, Annex I).

What has to be considered an adverse effect on the environment is technically defined in guidance documents, e.g., the guidance documents on information requirements and on the preparation of the chemical safety report (ECHA 2008). Just as with biocides, the approach is to protect the most sensitive species against effects of long-term exposure by applying the ecosystem threshold principle.

Priority substances under WFD

The general objective of Directive 2000/60/EC, the Water Framework Directive (WFD, EC 2000a), is to achieve a minimum ''good ecological status'' for natural waters and a ''good ecological potential'' for heavily modified and artificial waters by 2015. One criterion for this objective is the chemical state of the water bodies, i.e., the concentration of different chemical pollutants. To this end, Environmental Quality Standards (EQS) have been set up for 33 priority substances, which should not be exceeded. The EQS define the environmental objective of ''good surface water chemical status.'' The most important standards for the present discussion are those for the pelagic community: the Annual Average EQS (AA-EQS) should not be exceeded by the arithmetic mean of the measured values over a year, while the Maximum Acceptable Concentration (MAC-EQS) should not be exceeded by a single measurement. As a consequence, ''the AA-EQS and the MAC-EQS are intended to protect the structure and function of the addressed aquatic ecosystems from significant alterations by the impact of chemical substances'' (Lepper 2005). In addition, criteria can be set up for suspended matter, sediment and biota, depending on the properties of the substance.

The standards have been derived from the analysis of available data using the methods described in the Technical Guidance Document (TGD, EC 2003) and, because some of the priority substances are plant protection products, under Directive 91/414/EEC. Details are given in Lepper (2005), who also discusses the difference between the registration of plant protection products under Directive 91/414/EEC and the EQS setting under the WFD: ''Peak concentrations will normally be lower in the water courses that drain an agricultural area, than the initial concentration in a ditch adjacent to the application area. However, exposure of these draining water bodies may not cease as quick as in the ditch. Therefore, the recovery potential of aquatic ecosystems cannot be taken into account for the purpose of setting an annual average quality standard because exposure in draining water bodies is not transient, but will prevail for at least the use period of the active substance in the river basin.''

For other substances (not plant protection products), the main difference in EQS setting compared with PNEC derivation according to the TGD (EC 2003) is that the MAC-EQS explicitly considers acute scenarios, while the TGD (EC 2003) only considers chronic exposure. The current EQS for inland and other surface waters are listed in the Directive 2008/105/EC on environmental quality standards in the field of water policy, (EC 2008b).

With respect to protection aims, it is interesting to note that the WFD considers not only the chemical state of the water bodies but also their ecological status, which is defined as ''an expression of the quality of the structure and functioning of aquatic ecosystems associated with surface waters'' (EC 2000a). Here, biodiversity is explicitly considered by including

[4] ''The environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit it should be envisaged. In any event this impact should not constitute a criterion for refusal of a marketing authorization'' (EC 2004b).

[5] ''The environmental impact should be studied and consideration should be given on a case-by-case basis to specific provisions seeking to limit it'' (EC 2004c).

the composition and abundance of aquatic phytoplankton, flora, and benthic invertebrate fauna, and the composition, abundance, and age structure of fish fauna as quality elements in the classification of ecological status. Good ecological status is defined as follows: ''The values of the biological quality elements for the surface water body type show low levels of distortion resulting from human activity, but deviate only slightly from those normally associated with the surface water body type under undisturbed conditions'' (EC 2000a). As such, the WFD is the only directive considered here which has defined target images for ecosystems.

RISK CHARACTERIZATION APPROACHES

As shown above, the protection goals are only stated in qualitative terms and sometimes in very vague wording. This section, therefore, presents an overview of the data required and the way they are used in the different directives to achieve their protection goals. We use the aquatic risk assessment as an example, because the freshwater compartment is considered in all directives.

In principle, all risk assessment schemes are tiered, and the tiers are triggered by the mode of action, other substance properties or the volume (or mass) of a substance produced in or imported into the EU per year, as well as the outcome of lower tiers. The data requirements can be categorized into standard acute (e.g., for *Daphnia* and fish) or chronic tests (e.g., algal growth inhibition test) according to OECD test guidelines and higher-tier approaches with more flexibility (Table 1). In addition, bioconcentration and secondary poisoning are considered in all regulations, but slight differences exist in terms of triggering a fish bioconcentration study based on the K_{OW} of the substance and some additional substance properties.

The risk characterization approach is also very similar in the different directives, because it is based on the quotient of a Predicted Environmental Concentration (PEC) or measured concentration under the WFD and an ecological threshold value. The calculation of the PECs for the different types of substance is not discussed here; for more information, see, e.g., SANCO (2001, 2005) for plant protection products or EC (2003) for industrial chemicals. In all directives, except the plant protection product directive, a risk quotient, or rather hazard quotient (HQ), is calculated as follows: HQ = PEC / PNEC, where the PNEC is the Predicted No Effect Concentration derived from the endpoint of the most sensitive ecotoxicological test, divided by an assessment factor which should cover the remaining uncertainty in extrapolating from the test to the field situation. A potential hazard is indicated if PEC / PNEC > 1. The quotient for plant protection products[6] is defined the other way around and called Toxicity Exposure Ratio:

$$\text{TER} = \text{Ecotox endpoint}/\text{PEC}$$

The TER is compared with a trigger value corresponding to the assessment used for PNEC calculation. Thus, a potential hazard is indicated if the TER is below the trigger value.

The magnitude of the assessment factor or trigger value to be used depends on the number and quality of the available ecotoxicological tests. It is usually 10, 100, or 1000 for standard tests, but it might be lower than 10 for higher-tier tests. The uncertainty rates and trigger values to be used under the different directives are summarized in Table 2.

AQUATIC DATA REQUIREMENTS

Plant protection products

In view of the known (and intended) intrinsic toxicity of plant protection products and their intentional use in the open environment, these pesticides require a relatively large standard aquatic toxicity dataset, supplemented by different approaches to higher-tier testing. For example, in contrast to the other directives, Directive 91/414/EEC always requires 2 acute fish tests (Table 1). Depending on the mode of action, there must also be tests on an invertebrate additional to *Daphnia* or an additional algae species and *Lemna* as a macrophyte. Chronic tests are required if the substance does not dissipate very rapidly (i.e., dissipation time for 50% of the initial concentration (DT50) < 2 d) or the substance is applied more than once per season. If the TER, based on the standard test, does not exceed the trigger value laid down in the Uniform Principles of Annex VI of Directive 91/414/EEC, different options for higher-tier testing may be used, as discussed at the HARAP workshop (Campbell et al. 1998) and described in the Guidance Document (SANCO 2002). These tests include additional species testing in the laboratory, as well as microcosm or mesocosm studies. No official guidance is available on the trigger value to be applied to the results of these tests, but some recommendations have been made (e.g., Brock et al. 2006; De Jong et al. 2008). The use of such tests as compared to other directives reveals the following aspects that are specific for aquatic higher-tier testing under 91/414/EEC:

1) Additional species tests for Species Sensitivity Distributions (SSDs) of plant protection products are usually not designed to represent a wide taxonomic range. In fact, these tests focus on the most sensitive group, if this group can be identified from the product's mode of action. Thus, SSDs for insecticides should be based on insects and crustaceans, and those for herbicides on algae and macrophytes (Maltby et al. 2005; van den Brink et al. 2006). The most sensitive taxonomic group for fungicides may not be so easy to define, necessitating a test strategy similar to that for other chemicals (see below).
2) Because the exposure of nontarget species in edge-of-field water bodies is often variable in time as a result of drift, drainage, or runoff followed by dissipation, SSDs based on acute toxicity data may be appropriate. However, the other directives usually focus on a more or less continuous exposure, and thus prefer NOECs that are derived from chronic tests.
3) Microcosm and mesocosm studies are conducted as static studies with one or more applications depending on the use pattern of the plant protection product. The exposure pattern is thus characterized by one or a few entries followed by dissipation, and the final risk assessment can consider not only the effects but also the recovery of the affected populations. Two types of endpoints are often derived from such studies: an ecosystem NOEC as the highest concentration without any effects on structure and function, and a study-specific NOEAEC (No Observed

[6]Actually under 91/414, the TER is used for most groups, e.g., aquatic and soil organisms, birds, mammals, but, e.g., for honey bees, the HQ approach is used. In a recent EFSA opinion (EFSA 2009) the general use of the HQ=PEC/PNEC is recommended to achieve consistency with other regulations.

Table 1. Data requirements for aquatic environmental risk assessment for different classes of chemicals in the European Community[a]

Toxicity test	OECD guideline or guidance doc	Biological level	Dir 91/414/EEC	Dir 98/8/EC	Dir 2001/83/EC	Dir 2001/82/EC	Reg 2006/121
			Plant protection products	Biocidal products	Human medicinal products	Veterinary medicinal products	Industrial chemicals
Acute standard tests							
Daphnia	202	O	**Always**	**Alternatively marine/ brackish crustacean or mollusk if appropriate**	No acute tests	Tier A (freshwater or saltwater, depending on product)	> 1 t/a
Insect (e.g. *Chironomus*)		O	Insecticides with specific MoA	No	No acute tests		
Fish	203	O	**Always 1 cold + 1 warm water spec**	**1 or 2 species** (freshwater and marine)	No acute tests	Tier A (freshwater or saltwater, depending on product)	> 10 t/a
Chronic standard tests							
Algal growth inhibition test	201	P	**EC50 for green algae always required**	**1 or 2 species**	Tier A (NOEC used) Bluegreens for microbial products	Tier A (EC50), Tier B (NOEC) freshwater or saltwater species	> 1 t/a
Additional algal test	201	P	A non-green alga for herbicides and growth regulators	If necessary on the basis of expert judgment, e.g. marine macroalgae			
Daphnia reproduction test	211	O (P)	DT50 > 2 or n_appl > 1	If long-term exposure, not necessarily *Daphnia*	Tier A	Tier B	> 100 t/a
Fish growth, survival	210, 212, 215	O	DT50 > 2 or n_appl > 1	If long-term exposure	Tier A (Early Life Stage test)	Tier B Early Life Stage test preferred	> 100 t/a
Lemna growth	221	P	Herbicides and growth regulators	Based on expert judgment			
Additional invertebrate, e.g. *Chironomus* emergence	218/219	O	If substance may end up in sediments	Based on expert judgment	Tier B *(Chiro., Hyalella, Lumbriculus)*	Tier B	> 1000 t/a

(*Continued*)

Fish bioconcentration	305		Log K_{OW}>3 and (DT50>10 d or n_appl>1)	Log K_{OW}>3 or risk of secondary poisoning to predators	Tier B if e.g. log K_{OW} > 4.5, see TGD	Tier B if e.g. log K_{OW} ≥4, see TGD	> 100 t/a
Higher-tier tests							
Modified single species tests	HARAP[b]	O	e.g., test including sediment	Not mentioned explicitly	Not mentioned, unlikely to be conducted because not necessary for authorisation	Not mentioned, but possible in principle as mentioned in TGD	Not mentioned explicitly
Additional species (SSD)	GDAE[c], TGD[d]	O	Focus on most sensitive group according to mode of action	Not mentioned in the Technical Notes for Guidance but in the TGD			10 species of large variety of taxa required (see TGD)
Microcosm / Mesocosm	OECD, GDAE	P, C, E					Mentioned without specific guidance in the TGD

O = organism (survival, development, growth, reproduction); P = population; C = community; E = ecosystem.
[a]Bold entries indicate tests which are always required.
[b]Higher-tier Aquatic Risk Assessment for Pesticides (Campbell et al. 1998).
[c]Guidance Document on Aquatic Ecotoxicology under Directive 981/414 EEC (SANCO 2002),
[d]Technical Guidance Document (ECB 2003),

Table 2. Assessment factors used to calculate PNECs (Predicted No Effect Concentration) or trigger values for comparison with the TER (Toxicity Exposure Ratio) under different European schemes for chemical risk assessment

Assessment factor or trigger	Dir 91/414/EEC	Dir 98/8/EC	Dir 2001/83/EC	Dir 2001/82/EC	Reg 2006/121	Dir 2000/60/EC	
	Plant protection products	Biocidal products	Human medicinal products	Veterinary medicinal products	Industrial chemicals	AA-EQS[a]	MAC-EQS[b]
1000	Not used	3 L(E)C50s[c] of algae, *Daphnia*, fish	Not used	2 L(E)C5 for invertebrate and fish	3 L(E)C50s of algae, *Daphnia*, fish	3 L(E)C50s of algae, *Daphnia*, fish	Not used
100	Acute L(E)C50 of *Daphnia* or fish	One chronic NOEC[d] of invertebrate or fish	Not used	EC50 for algae	1 chronic NOEC of invertebrate or fish	1 chronic NOEC of invertebrate or fish	3 L(E)C50s of algae, *Daphnia*, fish
50	Not used	Two NOECs (algae, invert., fish)	Not used	Not used	2 NOECs (algae, invert., fish)	2 NOECs (algae, invert., fish)	Not used
10 - 100	SSDs[e] based on acute data	Not used	Not used	Not used	Not used	Not used	Substances with low interspecies variation due to known non-specific MoA
10	Chronic NOEC of invert. or fish, EC50 of algae or plant	3 NOECs of algae, invert. and fish	3 NOECs for algae, invert. and fish	NOECs for algae, invert. and fish	3 NOECs (algae, invert. and fish)	3 NOECs (algae, invert. and fish)	HC5 based on acute data
< 10	HC5[f] based on NOECs, microcosm/ mesocosm NOEC or NOEAEC[g]	HC5 based on NOECs, microcosm/ mesocosm-NOEC	not mentioned	not mentioned	HC5 based on NOECs, microcosm/ mesocosm-NOEC	HC5 based on NOECs, microcosm/ mesocosm-NOEC	Microcosm/mesocosm NOEAEC

[a]Annual Average Environmental Quality Standard.
[b]Maximum Acceptable Concentration.
[c]Lethal or Effect concentration for 50% effect.
[d]No Observed Effect Concentration.
[e]Species Sensitivity Distribution.
[f]HC5 = Hazardous Concentration for 5% = 5th percentile of an SSD.
[g]No Observed Ecological Adverse Effect Concentration.

Ecologically Adverse Effect Concentration, SANCO 2002) as the highest concentration at which the affected endpoints showed recovery within an acceptable time frame.

Biocidal products

According to the Technical Notes for Guidance on data requirements in support of Directive 98/8/EC (EC 2000b), the requirements for biocidal products are divided into core data and additional data. Core data are required for all product types and include acute tests on an invertebrate (*Daphnia* or other), 1 or 2 fish species (freshwater and saltwater) and an algal growth inhibition test (Table 1). Additional information is required if the acute data indicate a risk. Such cases may also require records specific to a particular product type, which are standard requirements for some product types for which long-term exposure is expected. Thus, a chronic test on reproduction and growth of a fish and an invertebrate and a growth inhibition test on algae (if no NOEC data are available from the core dataset) are necessary. Aquatic toxicity tests for other product types have to be additionally performed with marine or brackish species, if data are not available from the core dataset (e.g., for antifouling products). Additional data for other nontarget organisms like *Lemna*, marine macroalgae or sediment dwelling organisms can be required on the basis of expert judgment. The basic tool used in decision making is the PEC/PNEC ratio, and the risk assessment for the environment follows the methodology outlined in the TGD (EC 2003), with assessment factors ranging from 1000 for acute L(E)C50 values to 10 if at least 3 chronic NOEC values are available. Values below 10 are possible, based on a case-by-case decision, if SSD or microcosm/mesocosm data are available.

Medicinal products

In contrast to plant protection and biocidal products, not all medicinal products require a full aquatic risk assessment (Table 1). Instead, the risk assessment is triggered by a rough assessment of exposure and substance properties, known as Phase I, estimation of exposure. Phase II, the analysis of fate and effects, is only required if the PEC in water or (for veterinary products) soil is higher than a trigger value (e.g., 0.01 μg/L for human medicinal products) or the substance is considered to be also critical at lower doses due to its mode of action (e.g., cytostatics, substances with endocrine activity and antibiotics).

For human medicinal products, Tier A of Phase II requires 3 chronic tests (algal growth inhibition, *Daphnia* reproduction, and fish early life stage test (EMEA 2006)). The extended effect assessment in Tier B requires effects on a sediment-dwelling organism (*Hyalella sp*; *Lumbriculus sp*. or *Chironomus* sp.) to be examined, if the results of the water sediment study (e.g., OECD test 308) demonstrate significant shifting of the drug substance to the sediment. The EMEA guideline refers to the TGD (EC 2003) for details of the effect assessments.

For veterinary products, Tier A is based on acute tests (Table 1). Testing of 3 taxonomic levels is recommended, i.e., at least 1 fish, 1 aquatic invertebrate, and 1 algal species. Freshwater or saltwater species should be selected based on the use pattern of the product. Tier B is triggered when Tier A indicates a possible risk (HQ>1). In Tier B, effect studies are only recommended for biological compartments that do not pass the first tier. In addition, Tier B testing is recommended when bioaccumulation and sediment invertebrate toxicity is indicated.[7]

SSDs and microcosm or mesocosm studies are not explicitly mentioned in the guidelines for medicinal products but higher-tier studies are possible (SANCO 2003). The final risk characterization for both types of medicinal products is based on the PEC/PNEC approach.

Industrial chemicals

For chemicals regulated under REACH (EC 2007a), information requirements are laid down in Annexes VII–X. These requirements depend on the amounts of a substance manufactured in or imported into the European Community (more than 1, 10, 100, or 1000 ton/annum [t/a]). No ecotoxicological data are required for substances with less than 1 t/a. Above 1 t/a, at least an algal growth inhibition test and an acute *Daphnia* test must be provided (Table 1). Higher production or import volumes require other standard tests (see Table 2). Detailed guidance is given in the Guidance on Information Requirements and Chemical Safety Assessment (ECHA 2008). The PEC/PNEC approach and the assessment factors used to derive the PNECs correspond to those for biocides as laid down in the TGD (EC 2003). SSDs or model ecosystem studies with assessment factors on a case-by-case basis are listed as an option for refining the standard risk assessment: For example, an assessment factor in the range of 1 to 5 is applied to the 5th percentile of an SSD, based on NOECs preferably from at least 10 species and 8 taxonomic groups.

Priority substances

No data requirements are specified for the derivation of Environmental Quality Standards (EQS) for the priority substances, because the objective of the Water Framework Directive (EC 2000a) is not the authorization or registration of specific chemicals rather, it aims to assess the quality of water bodies in terms of contamination with chemicals. Thus, the EQS are derived from existing data. The way these data are used is mainly based on the methodologies outlined in the TGD for new and existing chemicals (EC 2003) and described in Lepper (2005).

IMPLICATIONS FOR THE POSSIBLE USE OF ECOLOGICAL MODELS

Based on the above comparison of protection goals, risk characterization approaches, and data requirements, we now define 5 main areas of application for ecological models and relate them to the different directives (Table 3). Case studies

[7] "The log $K_{ow} \geq 4$ is used as a criterion for an assessment of bioaccumulation. If the HQ for aquatic invertebrate is ≥ 1 it is recommended to consider the $PEC_{sediment}$/$PNEC_{sediment}$ ratio. The $PNEC_{sediment}$ is calculated using equilibrium partitioning. This method uses the $PNEC_{aquatic}$ invertebrate and the sediment/water partitioning coefficient as input. If the HQ is ≥ 1, then testing of sediment organisms is recommended. For substances with a log $K_{ow} > 5$, the HQ is increased by an extra factor of 10 to take account of possible uptake by means of ingestion of sediment. If the HQ is >1, then a study, preferably long-term, with benthic organisms using spiked sediment is recommended" (EMEA 2004).

Table 3. Areas of application for ecological models under different European schemes for chemical risk assessment[a]

Substances	Plant protection products	Biocidal products	Human medicinal products	Veterinary medicinal products	Industrial chemicals	Priority substances under WFD
EU directive	Dir 91/414/EEC	Dir 98/8/EC	Dir 2001/83/EC	Dir 2001/82/EC	Reg 2006/121	Dir 2000/60/EC
Most relevant protection principle	Community recovery	Ecological threshold	Not clear, hardly any restrictions	Ecological threshold	Ecological threshold	Ecological threshold
Population level consequences	X	X	X	X	X	X
Exposure profiles	X	(X)		(X)		
Recovery	X	(X)		(X)		(X)
Indirect effects	X	(X)		(X)		
Bioaccumulation	X	X	X		X	X

[a]X = direct link to the current protection principle; (X) = potential use if the community recovery principle is accepted for specific exposure situations.

for each of the application areas are presented in the second part of this review (Galic et al. this issue).

Extrapolation to the population level

Most of the routinely required tests provide data at the level of the individual organism (Table 2), in terms of survival, growth, and development and reproduction. Only the algal and *Lemna* tests provide direct population-level endpoints (inhibition of the population growth rate). The primary endpoint for the chronic *Daphnia* test is the inhibition of reproduction, but the intrinsic population growth rate can be calculated from life-table data. Population studies with single species are rarely conducted for risk assessment, but microcosm and mesocosm studies are often used to refine the risk assessment for algae, macrophytes or invertebrates in the context of 91/414/EEC, providing information at population, community and ecosystem levels. Thus, while the protection aims focus on the population (or higher) level, most data relate to the level of the organism. However, ecological models, i.e., population models, can potentially increase the ecological relevance of predictions by combining data on toxicity and bioconcentration with available knowledge about the ecology of species. Thus, such an approach may provide information about population-level consequences of effects on the individual level in terms of survival, development or reproduction (Forbes et al. 2009). Hence, extrapolation to the population level is considered here as the first and perhaps most promising area for the use of ecological modeling in chemical risk assessment, because models could easily translate test endpoints into protection goals. This will often include species-to-species extrapolation if the test species is not the species to be protected in the environment. The purpose might for example be to extrapolate from the inhibition of reproduction in the life-cycle test with the zebra fish to effects on stickleback populations in European water bodies. In such cases, the uncertainty of the extrapolation of species sensitivity has to be considered, for example, by an uncertainty factor applied to the toxicity data of the test species. For example, if only the standard tests are available, the default safety factor would have to be applied to estimate the LC50 used in the population model. If additional species have been tested, the factor might be reduced as would also be done for the usual risk assessment. Examples for the analyzing the consequences of effects on life cycle traits on population level endpoints can be found in Forbes et al. (2001) and Stark et al. (2004).

Extrapolation between exposure profiles

As a worst-case scenario, it is usually intended to keep exposure constant in standard ecotoxicological tests using semi-static or flow-through conditions. However, exposure patterns in the field may be variable and complex, especially for plant protection products entering edge-of-field water bodies (Brock et al. 2009). For example, different entry routes like spray drift, runoff, and drainage can lead to multiple entries into a water body from the application of the product itself, while degradation, transport, and dissipation of the substance might result in a much shorter exposure than the experimentally considered one. The FOCUS models used for PEC calculation of plant protection products in Europe calculate exposure profiles for different types of water bodies (pond, ditch, stream) for 10 European scenarios, defined by climatic conditions and soil type (SANCO 2001, 2005). Higher tier tests, such as mesocosms, can simulate multiple entries, but for practical reasons, in most cases, only 1 exposure profile can be tested. Therefore, extrapolation of effects from tested to not tested exposure profiles is also an area where ecological models could be applied (Hommen et al. 2009). This is especially important for plant protection products. Additionally, similar tools might be useful for other situations where exposure can be highly variable in time.

Extrapolation of recovery processes

As outlined above, the environmental risk assessment of plant protection products is, in most cases, based on the community recovery principle. This means that the recovery potential of populations in the field has to be estimated based on their life-cycle traits, interactions with other species, dispersal potential, and landscape characteristics. Experimentally, recovery can be tested only with some restrictions. For example, the design of a microcosm or mesocosm study may

inhibit recolonization by a species, necessitating extrapolation to the recovery under field conditions.

Analysis and prediction of indirect effects

If short-term direct effects are considered acceptable, as under the Community Recovery Principle, there may be indirect effects on other populations due to changes in predator–prey or competitive relationships, or changes in habitat structure. These types of effects can be analyzed in microcosm or mesocosm studies or terrestrial field or semi-field tests, but extrapolation to other types of communities or conditions might be needed. In addition, the interpretation of such complex studies might benefit from ecological modeling for the purpose of testing different hypotheses. In other cases, experimental testing of possible indirect effects may not be possible, e.g., if the dynamics of long-living animals have to be examined. If the more liberal Functional Redundancy Principle is applied, effects on single species or groups of species can even be more prolonged, increasing the likelihood of indirect effects, which—in the end—might also affect the ecosystem function. By contrast, the Ecosystem Threshold Principle aims to avoid the most sensitive species being affected, which would exclude indirect effects. In practice, however, it will be impossible to define the most sensitive species (see, e.g., Cairns and Niederlehner 1987), so an analysis of possible indirect effects might be useful even under this principle.

Prediction of bioaccumulation

In addition to the direct measurement of chemical effects on organisms and populations, all directives and regulations consider bioconcentration (uptake directly from the medium, e.g., water) and biomagnification (uptake by means of food) as indictors for possible long-term effects and secondary poisoning in the food chain. For plant protection products and biocides, a bioconcentration factor (for fish) $\leq$ 1000 is required for readily biodegradable substances and one $\leq$100 for those which are not readily biodegradable. Just as for the standard ecotoxicological tests, a refinement is possible (EC 2004a). Under REACH (EC 2007a), a substance meets the bioaccumulation criterion (B-) if the bioconcentration factor (BCF) is higher than 2000. Regulations for veterinary medicinal products only state that a regulatory guidance should be sought if the BCF is >1000 (EMEA 2004). In regard to plant protection products, food chain modeling is explicitly recommended for substances with high bioconcentration factors.[8] Because bioaccumulation is an important endpoint in the other directives as well, food chain modeling can also be recommended for the risk assessments of other chemicals.

RECENT DEVELOPMENTS AND OUTLOOK

All directives relating to risk assessments of specific classes of chemicals or products use more or less complex models to calculate the concentrations of the substances in environmental compartments, and guidance documents for different standardized exposure models have been produced (e.g., SANCO 2001, 2005). However, ecological models, e.g., population models, are rarely mentioned in the directives and related guidance documents. Only the guidance document relating to aquatic ecotoxicology under Directive 91/414/EEC (SANCO 2002) lists ecological models as a possible tool in higher tiers of risk assessment for extrapolation from microcosm or mesocosm studies to the field. Because it is not the absence of any effect but the vulnerability, resilience, and recovery potential of populations which are subjects of evaluation, there is clearly a potential for the application of population and ecosystem models in the risk assessment of plant protection products. For example, recovery of univoltine species can usually not be demonstrated in micro- or mesocosms due to the absence of recolonization in these isolated and small systems. In such a situation, population models may be used to demonstrate the potential of recovery (PSD 2003), as shown for the water louse *Asellus aquaticus* in van den Brink et al. (2007).

Recently, 2 SETAC workshops discussed the pros and cons of ecological modeling for risk assessment under Directive 91/414/EEC: the LEMTOX workshop offered a general elaboration of the benefits of and obstacles to ecological modeling in this area and discussed ways to overcome its shortcomings in the future (Forbes et al. 2009; Thorbek et al. 2009), while the ELINK workshop focused on the problem of extrapolating effects measured for 1 specific exposure pattern to the variety of exposure patterns predicted by FOCUS step 3 models (Brock et al. 2009). In view of the possibility of indirect effects if short-term direct effects are accepted, and the necessity to assess bioaccumulation within the food chain, the risk assessment of plant protection products would benefit from an increased use of ecological models in all 5 application areas.

In view of their great similarity in terms of protection principles, data requirements, and approaches to risk characterization, we discuss biocides, pharmaceuticals, industrial chemicals, and priority substances under WFD together here. In most cases, the main difference with the plant protection products is the basic assumption of a more or less prolonged, constant exposure. As a consequence, the protection goal is based on the Ecosystem Threshold Principle, i.e., avoiding any unacceptable effect from such long-term exposure. Therefore, extrapolation to variable exposure over time or prediction of recovery after short-term exposure is usually not an issue, and the main areas for the application of ecological models would be extrapolation to the population level and prediction of bioaccumulation. We are not aware of ecological models being recommended in official documents (e.g., Guidance Documents) relating to these classes of substances. However, the open literature offers several examples of applications of ecological modeling to substances other than plant protection products (see Galic et al. this issue), and some of the possible benefits of ecological modeling under 91/414/EEC also apply to other substances if ecological models are considered as a higher-tier tool to refine the assessments based on experimental data. For example, short-term exposure to products other than plant protection products sometimes has to be analyzed: the MAC-EQS under the WFD is intended to protect against effects of short-term exposure. Short-term exposure of aquatic ecosys-

[8]"If these triggers are met, detailed food chain modeling (e.g., according to Carbonell et al. 2000) should be performed, or micro- or mesocosm studies, which implicitly take into account biomagnification, should be submitted. However, it should be carefully considered whether the models used are appropriate for the special type of exposure relevant for plant protection products. If a modeling approach is selected, a food chain including at least three steps (algae, algae-feeding invertebrates, and invertebrates-feeding fish) should be considered" (SANCO 2002).

tems is also possible for some biocidal or veterinary medicinal products. If the Community Recovery Principle could be applied under these conditions, ecological models could be used to analyze, extrapolate, or predict the recovery of nontarget populations and could thus support decisions about the acceptability of a short-term effect.

Under the WFD, there might be another application area for ecological modeling, not related to the risk assessment of chemicals but to the comparison of different management options to improve the quality of a water body. For example, Capra et al. (2003) used a population model to analyze the effects of different discharge time series resulting from hydropower installation management on trout population dynamics.

Considering data requirements, we have shown that the type of data required for the different groups of chemicals is more or less the same, but the number of standard tests can vary as well as the frequency of use of SSD or model ecosystem data. The largest datasets can usually be expected for plant protection products, but there are also some other ''old'' substances for which large amounts of data are available. The use of toxicity data in population models usually requires dose-response data to translate concentrations into effects on life cycle traits, so NOECs which are often reported for chronic tests are not sufficient for this purpose.

In addition, ecological models not only require data on the intrinsic (species-specific) toxicity of a substance but also on the life-cycle properties of the focal species, as well as their environment and even the landscape for spatially explicit models. Thus, ecological models cannot be based on the data provided during the effect assessment itself but require additional ecological information. However, once a model has been developed and has been parameterized for a specific population or ecosystem and a specific substance, it is then relatively straightforward to use it for other substances as well, including those regulated under different directives. Therefore, research should analyze in greater detail if a limited number of ecological models can be parameterized for some species, representing different life-cycle types, and whether this can be useful for the ecological risk assessment of the different classes of substances regulated in the European Union. Which type of model might be appropriate for the different application areas and which additional data these models might need is analyzed in our second study in which we review existing models in terms of their potential use in chemical risk assessment.

Acknowledgment—This work was supported by the Cefic Long Range Research Initiative within the EPOCH (Evaluation of existing POpulation models for their potential application in ecological risk assessment of CHemicals) project (CEFIC Grant ECO10). The authors would like to thank Valery Forbes, Andrea Wenzel, Jan Klerkx, and Lara Ibrahim as well as the reviewers for valuable comments.

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