



Application of ERICA index to evaluation of soil ecosystem health according to sustainability threshold for chemical impact

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HIGHLIGHTS

- ▶ ERICA is able to harmonize cut offs and thresholds from different legislations and guidelines.
- ▶ The index can calculate effects of addition of a new compound into environment.
- ▶ Environmental fate and transport parameters were modified and improved.
- ▶ Two veterinarian pharmaceutical compounds and their metabolites are used as case studies.
- ▶ QSAR was used in case of missing and unreliable experimental data.

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ABSTRACT

The aim of the improved ERICA model for risk assessment (Boriani et al., 2010) is to give an instrument able to measure the effect of xenobiotics introduced into the environment. This will be of great help for “green” processes and sustainable industries and may help to advertise their products as safe for the environment following impact assessment. In this work we have added new indicators and scoring systems to be used in particular with attention for the soil compartment. Even though it is partly starting to be considered by some legislations, there is still an open debate to assess if a compound added to a certain scenario will increase risk for human beings and the environment. The prolonged environmental occurrence introduces uncertainty regarding the presence and properties of degradation products and cumulative effects from multiple substances present in the environment.

Tools capable of efficiently coping with this issue may prove useful for stakeholders. For instance, industries able to show that their substances present good characteristics also related to fate and transport properties may document the added value of environmental friendly products. Furthermore, the use of these tools may lead to awareness by industries of minimizing the environmental impact of the whole production chain. In the present study we show how the instrument ERICA may work by addressing multiple sources of exposure.

An improved version of ERICA and in particular its parameter EF (fate and transport of chemical compounds into the environment) is described in this paper and is applied to a scenario of two veterinarian pharmaceutical compounds: Sulfadiazine (SDZ) and Toltrazuril and their metabolites present in the environment. Results show that the new EF parameter is able to prioritize the chemical compounds better than the previous version with respect to their ability to degrade or not into the environment.

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1. Introduction

Addressing the risk of chemical mixtures in the environment is becoming increasingly complex, a fact acknowledged by the society (The Toxicologist, 2011). The European regulators have been very

active in the last years producing advanced regulations organizing the discipline of addressing impacts from exposure to chemical mixtures (e.g. REACH, 2006a, Water Framework Directive (WFD, 2000), the Marine Strategy Framework Directive (MSFD, 2008) and for pesticides Directive 91/414. Furthermore, there has been a wide debate on the preparation of the Soil Framework Directive (SFD, 2006). A new regulation has appeared for cosmetics (Commission Directive, 2008/42/EC of 3 April, 2008), and a world-wide effort has been promoted to achieve higher harmonization of regulations relative to chemicals, such as within the Globally Harmonised System (United Nations Economic Commission, 2009) with the purpose of protecting the environment and human health.

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The EU directive for industrial compounds (REACH) and their emissions into the environment, which also links to other Directives (WFD, SFD), require vast work for industries and regulatory bodies to assess the safety of the chemical substances. Moreover, the assessment of exposure of human populations and the environmental effects of these substances released into market and/or in the environment is requested by REACH supporting green, sustainable chemistry. This will result for instance in the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances during the whole life cycle of a chemical product.

A new strategic plan for chemical risk assessment has to address not only the single compounds, but also their interactions (Altenburger and Greco, 2009). In this direction recently the European Council of Ministers called for the necessary tools (EU Council, 2009) integrating and harmonizing risk assessment approaches for addressing the chemical emission within exposure scenarios as the reference to derive the risk of exposure to chemical mixtures adding a new component/activity. For this purpose, theories on the possible effects of chemical mixtures should be adopted. The elimination and/or reduction for emissions of new chemicals into the environment may be further driven by instruments such as ecolabelling of products and green public procurement (GPP) initiatives. The latter will promote the marketing of green and sustainable products (www.ecolabelling.eu) and reduce the emission of new compounds into the environment by reuse and recycling or design for degradation by purpose of eliminating continued accumulation of persistent pollutants within the environment. On this need the measure of concentrations of the prioritized harmful compounds into the environment followed by the use of the simple and concise ERICA (Boriani et al., 2010) will improve and help sustainable decisions.

ERICA is a tool for assessing the performance of chemicals during their life cycle, measured and modeled in terms for their cumulative impacts upon unintentional release into the environment. ERICA may quantify the territorial environmental quality as background for introduction of a new chemical into the environment and thereby support regional planning of new industrial activities like prior to realization of new planned projects (<http://ec.europa.eu/environment/eia/sea-legalcontext.htm>). ERICA has integrated all existing information on chemicals in the classical EU risk assessment scheme taking into account also alternative methods (in vitro, in silico) as required by the new EU Directives e.g. REACH, 2006a, and Cosmetic Directive (Van Leeuwen et al., 2007a, 2007b, 2009). ERICA provides a clear information and communication tool to regulators, stakeholders and the population about the possible chemical hazards in a site and their relative effects on ecosystems and human health. In the present study we show how the instrument ERICA may work by addressing multiple sources of exposure and their application to soil ecosystem health.

1.1. Case study on soil ecosystem health

In line with the idea behind ERICA, which is to build a modular and upgradable index, this paper presents some new theoretical indicators as part of the ERICA index, in particular to be used for the soil compartment in assessing the sustainable use of chemicals by preventing their accumulation in the environment. For example degradation is of extreme importance in the soil compartment to understand how the chemical will be transformed and how properties like persistency and mobility will be different in the case of metabolites of the parent compounds. The main aims of the scenario will be 1) to provide an assessment of the cumulative risk posed by various compounds of diverse origin and under diverse regulation, but all being present in top soils, 2) to calculate positive and negative effects of emitting a new compound into the environment and 3) to harmonize cut off and thresholds from different legislations and guidelines. Several compounds, regulated by different legislations and guidelines would indicate the need to be assessed and harmonized within a

unique methodology, with the ability to provide a holistic picture of a specific scenario according to territorial characteristics and history. For example the use of veterinarian pharmaceutical compounds resulting in their presence in manure spread on top soils and into the environment has been discussed and many risk assessment studies have been conducted; still there is a lack of knowledge regarding several environmental endpoints (Boriani, 2012). This is mainly due to the fact that only recently, i.e. in 2006, the European Medicines Agency (EMA) decided that all new marketing authorization applications for human and veterinarian pharmaceuticals should be accompanied by an environmental risk assessment of the release of veterinarian pharmaceuticals from contaminated manure amended to agricultural soils (EMA, 2006). The EMA risk assessment has a PEC/PNEC (predicted environmental concentration/predicted no effect concentration) approach and is divided into two phases similar to the general risk assessment scheme: Phase I includes collection of data on pharmaceutical concentration levels in the environment. In phase II, data on the substance's physico-chemical properties, persistence, bioaccumulation and ecotoxicity are reviewed and the PNEC is estimated. All relevant data should be taken into account. Experimental studies should preferably follow standard test protocols, but it is recognized that there are other acceptable methods. However, their use should be justified and studies should be conducted in compliance with good laboratory practices (GLP), e.g. OECD GLP, 2007. Due to the lack of data availability the use of predictive models is very helpful to close data gaps and to improve reliability and relevance of existing data. In fact, in some cases, only proprietary data are available; all the experimental data steps that lead to a certain final toxicological data are completely missing or censored (Gilbert, 2011).

1.2. Relationship between ERICA index with legislations and guidance

As already mentioned, different legislations and guidelines exist for regulating chemical use categories according to sectors. The different regulations impose or suggest limits and cut-off values for emissions and concentration reduction goals for chemicals that have been released into the environment. However, none of these regulations addresses the environmental quality of a territory as a whole and in this way they may all fail to protect environment and human health taking into account the actual exposure scenario including all points of exposures and sources contributing to the total exposure of the target receiving organism through multiple transport pathways.

Table 1 presents the main legislation/guidelines regulating xenobiotics released into the environment, providing an overall idea of their aims and compounds treated and in which environment.

For example within REACH (2006b) there is a requirement for environmental properties upon their possible release into the environment; the latter is part of the chemical safety sheet for each new and existing industrial. The Pharmaceutical Regulations of both human (http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf) and veterinarian (EMA, 2006) have recently integrated the safety part regarding the release of the pharmaceuticals into the environment and related to maximum residual limit (MRL) ([admitted in food. This regulation sets its boundaries to the intended use neglecting e.g. unintentional released through the use of manure as fertilizer and resulting the risk of freshwater contamination by surface runoff or groundwater and drinking water contamination by vertical soil infiltration and leaching.](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000165.jsp&mid=WC0b01ac058002d89b&jsenabled=true, n.a.)

The same thing happened with the pesticide directive. The use of pesticides in the environment is regulated. Furthermore, there are new regulations that will be released in the next years regarding environmental safety and production of nano products, biocides (e.g. antifouling compounds), endocrine disrupter's compounds and waste management.

Table 1
Summary of the main EU legislation regulating xenobiotics released into the environment.

Name legislation	Reference	Status	Main objectives
REACH regulation	(REACH, 2006a)	In force	Industrial compounds
Water Framework Directive	(WFD, 2000)	In force	Contaminants in the water
Marine Strategy Framework Directive	(MSFD, 2008)	In force	Protect and clean up EU coasts, seas and oceans
Pesticides directive	(Directive 91/414)	In force	Defining strict rules for the authorization of plant protection products (PPPs). The Directive requires very extensive risk assessments for effects on health and environment to be carried out, before a PPP can be placed on the market and used. Community rules also exist that define maximum residue limits (MRLs) on food- and feedstuffs.
Biocide Directive	(Directive 98/8/EC)	Under preparation	Aims to harmonize the European market for biocidal products and their active substances.
Soil Framework Directive	(SFD, 2006). (Commission Directive 2008/42/EC of 3 April, 2008)	Under preparation	Its objective is to protect soils across the EU
Globally Harmonised System	(United Nations Economic Commission, 2009)	In progress but still old system and new system together till 2015	Aim of the GHS is to have, worldwide, 1) the same criteria for classifying chemicals according to their health, environmental and physical hazards; and 2) the same hazard communication requirements for labeling and safety data sheets.
Ecolabelling of products and green public procurement	(GPP initiatives)	Voluntary instrument	Process whereby public authorities seek to procure goods, services and works with a reduced environmental impact throughout their life cycle when compared to goods, services and works with the same primary function that would otherwise be procured
Pharmaceutical Regulations	Human	In force	Find regulatory and procedural advice on marketing authorizations, pediatric investigation plans, orphan designations, scientific guidelines, information on advisory services including scientific advice, the micro, small and medium-sized enterprise (SME) office and the innovation task force, inspections and fees.
Pharmaceutical Regulations	Veterinarian	In force	Find regulatory and procedural advice on marketing authorizations, maximum residue limits, scientific guidelines, information on advisory services including scientific advice and the micro, small and medium-sized enterprise (SME) office, referrals, inspections and fees.
OSHA guidelines	Part 1910 – Occupational Safety and Health Standards	In force	Assure safe and healthful working conditions for working men and women by setting and enforcing standards and by providing training, outreach, education and assistance.

Furthermore we can mention the Global harmonize systems (GHS) “Globally Harmonized System of Classification and Labelling of Chemicals” that addresses in a word scale classification of chemicals according to types of hazard and proposes harmonized hazard communication elements, including labels and safety data sheets. The GHS aims at ensuring that information on physical hazards and toxicity from chemicals is available in order to enhance the protection of human health and the environment during the handling, transport and use of chemicals. The GHS also provides a basis for harmonization of rules and regulations on chemicals at the national, regional and worldwide levels, an important factor also for trade facilitation. At present, for example, in the case of occupational risk assessment each nation has individual occupational rules and limits that rarely are similar and a uniformed legislation will be more and more required with the free movements of people and goods (OSHA guidelines).

This premise is to explain in our opinion that the aim of the ERICA Index is not to be a substitution to any regulation or guidance, but it can be an important help and a supportive documentation to prioritize harmful compounds. Furthermore it can help in understanding the harmful effects to human and environment upon exposure to a cocktail of chemicals that are part of the same scenario but falling into diverse directives and regulations. Most importantly, ERICA is able to provide a holistic picture of territorial environmental qualities as a function of existing chemical air emissions, waste and wastewater flows. ERICA can provide guidance for future innovative resource management systems with the ability to improve environmental qualities for the provision of equity in the availability of high quality resources for future generations. Furthermore, ERICA may provide a means of documenting green technology networks for remediation of historical and/or reduction of future emissions to a level where environmental detoxification exceeds the rate of emissions, i.e. the level of sustainable industrial emissions.

For example a veterinarian pharmaceutical compound is handled during some stage of farming poultry and afterwards unintentionally released into top soils via manure. Still, the pharmaceutical regulation of the compound is restricted to protect people in respect to food

intake (where maximum residue levels are established) and from here a maximum allowed quantity to cure the animals is set. The new pharmaceutical regulation also includes a risk assessment to avoid any harmful known effect to humans and the environment in the scenario of use of contaminated manure as soil fertilizer and the resulting release of pharmaceuticals into the environment. In spite of these improvements, there may still be pesticides present in the land use scenario because it is an agricultural soil. Additionally, in a former vicinal industrial area there may be a release of compounds like dioxins, metals that are still present in the soil due to specific physico-chemical properties of the pollutants. At this stage ERICA is able to build up a schema of possible risk or avoided risk adding to a certain territorial scenario where some contaminants are already present, by including or excluding one or more compounds. Of course all the mechanisms and synergies will not be explained, due to the complexity of the intrinsic mechanisms. However ERICA is able to give a general picture of the overall situation, across any regulation and any imposed limit. This will support the needed steps into new strategies towards a sustainable economy where the addition of a new compound into the environment will not pose any risk for the scenario. Different legislations provide guidance that focuses on a particular phase of the risk assessment and lists particular endpoints. The challenge of regulation on chemicals is the concept of integrated risk assessment and management. Integrated risk assessments are necessary for dealing successfully with cumulative risk from multiple stressors. Integration can, however, be framed and conceived in different ways by stressing various aspects (Assmuth and Hildén, 2008; Glenn et al., 2011). For example, in regards to soil ecosystem health, inputs from the planned EU soil directive (EU Directive, 2006) were taken into account as described in the following paragraphs choosing new indicators from OECD guidance documents and recent publications (Thomsen et al., 2011).

We propose an improved framework for addressing environmental quality to plan future eco-industrial activities for sustainable management of natural resources. To provide high quality ecosystem services, we believe that a holistic description of environmental

qualities is necessary for adopting the right risk measured needed to move towards increased restoration and resiliency of ecosystems and global patterns in environmental burden of diseases threatening the life quality of future generations.

2. Material and methods

2.1. Set scenario of chemical compounds present in the environment

The minimum scenario is composed of priority compounds released or emitted into the environment; also waste management process should be considered. A data inventory of the principal contaminants in the environmental compartments from the local emissions is firstly performed, enlarging the completeness in the existing ERICA database to include territorial characteristics. All the data related to environmental toxicity, human toxicity, human carcinogenicity, physico-chemical data, fate and transport (comprehensive of in vitro analysis, epidemiological study, speciation, metabolites, etc.) are collected. All available experimental data related to environmental and human endpoints are needed in this phase. Several toxicity databases are available. They address different endpoints, chemicals, and have different format. This is the list of the databases used in ERICA: ISSCAN; AMBIT; ECOTOX, HSDB; U.S. NIH ChemIdPlus; QSARWORLD; CPDB; FatePointer; CHEMSPIDER. To find reliable data and filling data gaps also predictive methods and database containing predicted data are used such as the VEGA platform; EPIsuite and Danish EPA.

2.2. How chemicals entry into a territorial scenario

The compounds are part of the scenario depending of the preliminarily characterization of the investigated site. All the information available should be used, such as industrial emissions and productivity of the catchment area and/or the site at risk of being contaminated with an additional chemical, type of waste management of the area, site specific history of previous contaminations, soil ecosystem structure and functioning, epidemiological evidences and ecological evidences, possible punctual sources of contamination, exposed receptors (human and ecological), the environmental level of the added pollutants. Reports and documents are very important in this phase, but also the study within a GIS (geographic information system) that contains many layers of information such as soil composition, meteorological data for the study of the spatial distribution of the contaminants as a result of leakages from combined technologies and resource flows crossing the human and natural system, such as air and water circulation (Lahr et al., 2010; Pizzol et al., 2012).

There is no limit to the number of chemicals assigned to a specific scenario. Still, the best is to prioritize the most relevant compounds with respect to the risk of potential cumulative impacts present in the local environment (harmful compounds, massive presence due to local industries), in order to approximate to the most realistic scenario, and on that basis add the chemical(s) of interest.

2.3. New indicators added to ERICA index

In order to build a model able to prioritize chemicals useful for regulatory purposes we added new indicators to the previous index EFI, covering the fate and transport parameters in the ERICA index. These new indicators are useful to get a more complete picture of how the compound is acting in the environment. Not all the indicators are available from the literature and some of them are calculated thanks to modeling techniques, the values for some indicators are derived, while the others are calculated. Furthermore the PEC_{initial} value is refined with an iterative process to the so called PEC_{final} depending on the transformations that can occur into the environment (in particular soil). In the case of missing and unreliable experimental data there is a modeling software available (see Section 2.5 on Modeling

resources). There are various properties that can be available for a compound or that can be calculated in order to improve the knowledge on its transformation and, consequently, its metabolites. Tables 2 and 3 provide physico-chemical properties and degradation studies that are often conducted while assessing a compound.

2.4. EF (environmental fate and transport) parameter modifications

The EF index, based on Eq. (1), represents a single value useful to get an idea of the potential long term influence of a chemical compound into the environment. The Environmental Fate of the toxicant (EF_{compound}) is related to the physico-chemical properties of the pollutants according to Eq. (1), quantifying the most important properties influencing the behavior of the xenobiotic in the environmental matrix. Therefore EF_{compound} represents a quantitative estimate of the environmental fate and transport of the compound; the minimum EF value for an ideal compound is equal to unity and the maximum EF value for an ideal compound is equal to 30 [see SI, scoring values Tables A–F].

A new, more suitable scoring system was adopted in order to classify better the compounds and their properties, in particular for Solubility and Photolysis we adapted the new scoring system from US EPA, 2011.

These modifications refine the maximum value that EF can assume and also its minimum value, as further explained.

The EF parameter was already present in ERICA but now it is improved with new parameters and a more precise scoring system. EF parameter in fact is a value that is multiplied in the ERICA index due to the fact that a substance is more dangerous if it presents characteristics to stay long time in the environment.

The formula to calculate EF compound is the following:

$$EF \text{ compound} = (S + M + Ph)/V + BCF + P. \quad (1)$$

The single components are now explained in details tracking changes with the previous version of EF:

- S is the solubility quantified as a relative compound-specific score value for the water solubility; the scoring system has been modified compared to the previous ERICA version as provided in the supplemental information [SI, Table A]. A new reference was used to better describe the solubility into the environment; in the previous index we used a scoring system related to the solubility referred to metabolism of the compounds into organisms.
- M is the score value for the mobility of the compound, which is based on Koc value [see SI, Table B];
- V is the score value for the volatility of the pollutants, based on its vapor pressure [see SI, Table C];
- BCF is the BioConcentration Factor, modified according to the ERICA version presented in Boriani et al. (2010) and expressed as the logarithm of the compound's BCF or BAF [see SI, Table D];

Table 2
Physico-chemical properties.

pKa (OECD 112)*
Melting point (OECD 102)*
Vapor pressure (OECD 104)*
Henry constant (OECD 305)*
Water solubility (OECD 105)*
Log Kow (OECD 107)*
Log Koc (OECD 106)*

*OECD guidance are available at OECD website: http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals_chem_guide_pkg-en.

Table 3
Degradation studies $PEC_{initial}$ value versus $PEC_{refined}$.

Dissipation DT50 (OECD 307 ^a)
Hydrolysis (OECD 112 ^a)
Soil photolysis (OECD 307 ^a)
Solubility (OECD 105 ^a)
Adsorption/desorption (Kd/Koc) (OECD 106 ^a)
Degradation (OECD 301 ^a)

^a OECD guidance are available at OECD website: http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals_chem_guide_pkg-en.

P is the score value for the persistence of the pollutant, quantified by the degradation time [see SI, Table E];
Ph is the score value for the photolysis [see SI, Table F].

In particular the addition of the new parameter Ph and the new scoring system as described above and in the SI improves the parameter EF (Environmental Fate and Transport index) Eq. (1); the physico-chemical property added to the definition of the EF subindex (Ph) is useful to describe the stability of a pollutant when it is released into an environmental matrix.

2.5. Modeling resources

Free platforms for assessing chemical properties and toxicity data using read across methodology and data mining technologies developed within the EU-projects ORCHESTRA (FP7 contract number 226521) and CAESAR (FP6 contract number 022674) (Benfenati, 2010) may be used for deriving input parameters need for ERICA. In particular the new free platform VEGA provides models for QSAR and read across for endpoints reported in Table 1. Furthermore VEGA platform provides a large report with the reasoning behind the model calculation considering the evaluation of the applicability domain and similarity within chemicals in the training set of the models. The evaluation is addressed according to the OECD principles: accuracy, sensitivity, specificity, false positives and false negatives.

2.6. Iterative process for assessing reliable PEC value

The predicted environmental concentration of a chemical that enters into the environment is refined in relation to the physico-chemical processes, degradation, fate and transport process that may occur. An initial derived PEC value, $PEC_{initial}$, is then processed into a refined PEC value ($PEC_{refined}$) as described in Fig. 1. Parameters of predictive environmental concentration are entered into ERICA after an iterative process where they gain increased reliability concerning their actual presence and availability in a specified territorial context. This procedure reduces uncertainties and increases the knowledge about the fate of the chemical. In Fig. 1 this process is schematized.

Degradation studies (Table 3) are all very useful to process $PEC_{initial}$ into $PEC_{refined}$, in case of missing or unreliable data for the majority of parameters there are modeling resources available as described in Table 4.

3. Case studies

3.1. Environmental risk assessment of pharmaceuticals

We have tried the new index on two cases of veterinarian pharmaceutical compounds: Toltrazuril (CAS 69004-03-1) and Sulfadiazine (CAS 68-35-9). These two substances are of augmented interest because they are found in increasing concentrations in the environment. Both the veterinarian pharmaceutical compounds of the present case study are considered compounds of concern within the top consumed 50 veterinarian pharmaceutical compounds by the prioritization methodology adopted by Capleton et al., 2006. This methodology is reassumed in the adapted table (Table 5).

Due to the fact that we had no data on environmental concentrations, we used the EF parameter, described in Eq. (1), as a classifier for the type of risk posed by these compounds.

EF parameter was already used (Riskcycle EU project, 2010) to prioritize lubricants, in a similar case where no data on environmental concentrations were available, and the EF classification was useful to prioritize the compounds to be added to the scenario.

The Capleton classification was made on the basis of the target treatment groups, routes of administration, and metabolism; the 50 pharmaceuticals were further evaluated for their potential to reach the environment (Stage I). Target treatment groups included live-stock, aquaculture applications, and companion animals.

The routes of administration considered grouped them into two categories: topical (T) and others (O). A pharmaceutical has a greater potential for entering the environment when it is applied topically compared to other applications. For other uses, metabolic rates for veterinary pharmaceuticals were collected from the literature and used to assess the potential for environmental release.

When a pharmaceutical is used for multiple target groups or when metabolism data were unavailable, the worst-case scenario was applied giving the highest rank. A further hazard assessment was undertaken for veterinary pharmaceuticals with a potential for entering the environment that was anything other than “low”.

In Stage II, ecological hazards and human health impacts were assessed for the veterinary pharmaceuticals identified in Stage I. According to the ecological or human health data, or both, the pharmaceuticals were divided into four groups that ranged from low (L) to very high (VH) hazard. Ecotoxicological information was gleaned from the available literature and used for deriving predicted no-effect concentrations (PNECs). In the absence of ecological toxicity data, human health impact information for each veterinary pharmaceutical was calculated from acceptable daily intake (ADI) values.

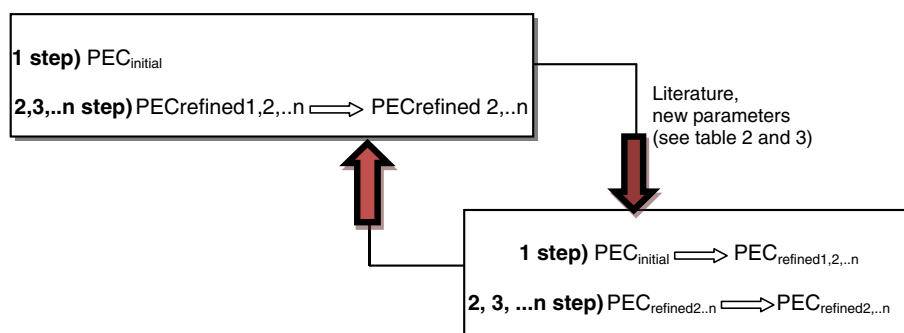


Fig. 1. Visualization of the process of improving $PEC_{initial}$ to derive at the $PEC_{refined}$ with the knowledge derived from physical chemical process.

Table 4

Freely available predictive models for calculating ERICA input parameters.
Adapted from ANTARES website, www.antares-life.eu.^a

Physico-chemical properties	Freely available models
pKa (OECD 112)	pKa (through OpenTox platform: ToxPredict) http://apps.ideaconsult.net:8080/ToxPredict EPISUITE (US EPA) http://www.epa.gov/opptintr/exposure/pubs/episuite.htm SPARC (University of Georgia) http://archemcalc.com/sparc VCCLAB (Virtual Computational Chemistry Lab) http://www.vcclab.org/
Melting point (OECD 102)	EPI Suite™ (US EPA) – module MPBPWIN v1.43 http://www.epa.gov/oppt/exposure/pubs/episuite.htm SPARC (University of Georgia) http://archemcalc.com/sparc T.E.S.T. (US EPA) http://www.epa.gov/nrmrl/std/cppb/qsar
Vapor pressure (OECD 104)	EPI Suite™ (US EPA) – module MPBPWIN v1.43 http://www.epa.gov/oppt/exposure/pubs/episuite.htm SPARC (University of Georgia) http://archemcalc.com/sparc
Henry constant (OECD 35)	EPI Suite™ (US EPA) – modules HENRYWIN v3 http://www.epa.gov/oppt/exposure/pubs/episuite.htm/
Water solubility (OECD)	EPI Suite™ (US EPA) – modules WSKOW v1.42 & WATERNT v1.01 http://www.epa.gov/oppt/exposure/pubs/episuite.htm OSIRIS property explorer http://www.organic-chemistry.org/prog/peo/ SPARC (University of Georgia) http://archemcalc.com/sparc T.E.S.T. (US EPA) http://www.epa.gov/nrmrl/std/cppb/qsar VCCLAB (Virtual Computational Chemistry Lab) http://www.vcclab.org/
Log Kow (OECD 107)	MLR model for Exp LogKow (through OpenTox platform: ToxPredict) http://apps.ideaconsult.net:8080/ToxPredict XLogP (through OpenTox platform: ToxPredict) http://apps.ideaconsult.net:8080/ToxPredict VEGA – free software for QSAR http://www.vega-qsar.eu/ EPI Suite™ (US EPA) – module KOWWIN v1.68 http://www.epa.gov/opptintr/exposure/pubs/episuite.htm SPARC (US EPA) http://archemcalc.com/sparc VCCLAB (Virtual Computational Chemistry Lab) http://www.vcclab.org/
Log Koc (OECD 106)	EPI Suite™ (US EPA) – module KOCWIN v2.00 http://www.epa.gov/oppt/exposure/pubs/episuite.htm/
<i>Degradation studies</i>	
Dissipation DT50 (OECD 307)	http://www.epa.gov/oppefed1/models/water/input_parameter_guidance.htm EPI Suite™ (US EPA) – module STP www.epa.gov/oppt/exposure/pubs/episuite.htm
Mobility (OECD 312)	http://www.epa.gov/oppefed1/models/water/input_parameter_guidance.htm EPI Suite™ (US EPA) – module Fugacity www.epa.gov/oppt/exposure/pubs/episuite.htm
Hydrolysis (OECD 112)	EPI Suite™ (US EPA) – module HYDROWIN v2.00 www.epa.gov/oppt/exposure/pubs/episuite.htm SPARC (University of Georgia) http://archemcalc.com/sparc
Soil photolysis (OECD 307)	http://www.epa.gov/oppefed1/models/water/input_parameter_guidance.htm http://www.epa.gov/oppt/exposure/pubs/episuite.htm module AOPWIN v1.92
Adsorption/desorption (Kd/Koc) (OECD 106)	BASL4 (Canadian Centre for Environmental Modelling and Chemistry) http://www.trentu.ca/academic/aminss/envmodel/models/BASL4110.html EPI Suite™ (US EPA) – module KOCWIN v2.00 http://www.epa.gov/oppt/exposure/pubs/episuite.htm
Degradation OECD301	START biodegradation and persistence plug-in (through OpenTox platform: ToxPredict) http://apps.ideaconsult.net:8080/ToxPredict CRAFT (JRC) http://www.molecular-networks.com/products/craft EPI Suite™ (US EPA) – modules BIOWIN v4.10 & BIOHCWIN v1.01 http://www.epa.gov/oppt/exposure/pubs/episuite.htm/
<i>Fate and behavior in the environment</i>	
BCF BioConcentrationFactor	VEGA – free software for QSAR http://www.vega-qsar.eu/ EPI Suite™ (US EPA) – module BCFBAF v3.01 http://www.epa.gov/oppt/exposure/pubs/episuite.htm CAESAR Project models (CAESAR Consortium) http://www.caesar-project.eu/ Fish model (Canadian Centre for Environmental Modelling and Chemistry) http://www.trentu.ca/academic/aminss/envmodel/models/Fish2.html T.E.S.T. (US EPA) http://www.epa.gov/nrmrl/std/cppb/qsar TAOBAC model (Canadian Centre for Environmental Modelling and Chemistry) http://www.trentu.ca/academic/aminss/envmodel/models/TAOV101.html

^a <http://www.antares-life.eu/index.php?sec=modellist>.

Both the compounds of the case study are present in the Capleton prioritization study (Capleton et al., 2006). Toltrazuril (TZ) has a metabolite, Ponazuril, and both the compounds are found in soils receiving manure deriving from animals treated with Toltrazuril. Sulfadiazine (SDZ) has two metabolites, as SDZ in manure is transformed into acetyl-SDZ and hydroxy-SDZ. However, since acetyl-SDZ is retransformed to SDZ,

mainly SDZ and hydroxy-SDZ is found in the soil. The structures are reported in SI, Table G.

The EF gives additional information compared to other prioritization system because it is a multifactorial parameter based on easy recoverable physico-chemical properties, each one taking into account a particular feature of the process of fate and distribution of a compound. In the

Table 5

Prioritization of veterinary medicine active ingredients for detailed risk assessment according to their potential for indirect exposure and their toxicity profile (adapted from Capleton et al., 2006).

Veterinary medicine active ingredient	CAS number	Therapeutic indication	Chemical group	Potential to reach the environment	Usage toxicity profile	classification	Priority for detailed risk
Toltrazuril (TZ)	69004-03-1	Coccidiocide	Triazinetrione derivative	High	Low (Usage data incomplete)	High	High
Sulfadiazine (SDZ)	68-35-9	Antibiotic MFA and antimicrobial	Sulfonamide	High	High	High	High

Table 6
EF with the previous (Boriani et al., 2010) and the new equation (Eq. (1)) are calculated for the case study compounds and all the values and score values of the physico-chemical properties that are input parameters for the final EF index are reported.

A												
Name	Fragment water solubility (estimated) [mg/l]	Score	Vapor pressure at 25 °C (estimated) [mmHg]	Score	LogKow (estimated)	Score	Koc – soil mobility Gustafson, 1989	Score	LogBCF (estimated)	Score	Photolysis AOPwin [days]	Score
Ponazuril	1.492E–03	1	4.35E–18	1	5.40	7	2.79	1	1.08	2	0.313	3
Toltrazuril	1.940E–05	1	1.68E–15	1	9.00E–02	3	1.70E+03	2	2.43	3	0.234	2
Sulfadiazine	7.700E+01	1	8.88E–07	1	5.80E–01	3	1.54E+02	3	5.00E–01	2	0.381	2
N-acetylsulfadiazine	4.564E+03	3	1.97E–10	1	3.90E–01	3	4.51E+01	5	3.80E–02	2	1.373	5
Hydroxysulfadiazine	3.747E+05	6	8.01E–13	1	3.00E–01	3	5.52E+01	4	5.00E–01	2	0.303	3
B												
Name	Mackay model level III fugacity AWS air	AWS water	AWS soil	AWS sediments	AWS water + sediments	Biodegradation (persistence)	Biowin 3 numeric	Biowin 3 timeframe	BioWin 6 probability	Persistence	Environmental fate and Transport EF ^a	Environmental fate and transport improved EF ^b
Ponazuril	7.510	4.320E+03	8.64E+03	3.890E+04	4.32E+04	1.800E–03	1.543	Recalcitrant	0.00	7	11	14
Toltrazuril	5.620	4.320E+03	8.64E+03	3.890E+04	4.32E+04	1.002	2.54	Recalcitrant	1.00	5	11	13
Sulfadiazine	9.570E–01	2.020E+01	7.86E+01	1.910E–01	2.04E+01	8.126E–01	2.70E+04	Weeks–months	3.54E–02	0	6	8
N-acetylsulfadiazine	3.080E–04	2.800E+00	7.61E+01	8.750E–02	2.89	3.631E+04	2.50E+04	Weeks–months	1.53E–02	0	10	15
Hydroxysulfadiazine	3.080E–04	2.380E+1	7.61E+01	8.750E–02	1.522E+02	5.030E–01	2.42	Weeks–months	6.90E–03	5	17	20

^a EF = ((S + M/V) + BCF + P).

^b EF improved ((S + M + Ph)/V) + BCF + P.

case where EF is high the compound or its metabolites will stay longer into the environment and pose an unknown possible concern for the future. Instead, if a compound and its metabolites degrade fast we should take care only about the present risk that it is posing.

3.2. Discussion

In the Table 6A and B it is possible to see that the improvements in EF scoring extend the range of values (1–30 instead of 2.67–25).

The higher the EF parameter is, the higher the probability that the compound will stay longer in the environment without being degraded and as a consequence this will lead to an increased risk of cumulative effects in time.

In ERICA (Eq. 9 from Boriani et al., 2010) the EF parameter is a multiplicative factor that indicates the potential danger of exposure on a time scales. This measure shows that the levels of a compound could rise over time, becoming a matter of concern for the future.

The EF parameter shows that the metabolites are more persistent in the environment than the compound SDZ and Toltrazuril. This is important in order to improve the investigation of the presence of the metabolites and their other possible adverse effects on the environment in a longer time scale.

As can be seen in Table 5, the Capleton prioritization study is good but limits the environmental and fate parameter to only one indicator: “Potential to reach the environment” and takes into consideration only the parent compound. Instead the EF parameter uses many physico-chemical properties in order to classify the compound. There are experimental data available for both the compounds but some are unreliable and largely variable, so in our analysis modeling data were also used.

Table 6A and B summarizes the calculated value of EF for each chemical. Both compounds show possible future risks related to their scarce mobility particularly for their metabolites Ponazuril and OH SDZ.

The information provided by ERICA and its EF_{compound} index contains many physico-chemical and degradation indicators not present in other prioritization systems such as the one presented in Capleton et al., 2006. Through the EF_{compound} ERICA has the possibility to measure how much the compound is staying into the environment and consequently to model if it will be degraded or not. So, the “detoxification rate” of a compound over time can be estimated and predicted by ERICA while other systems do not even consider it.

4. Conclusions

The strength of the improved ERICA methodology is its ability to verify whether an additional stressor may or may not cause further risk upon release to a specified environment compartment within a territorial context. As part of a concise methodology ERICA can be used as a prioritization system, while if a detailed risk assessment is needed it is possible to disaggregate and extract data from each step of ERICA model procedure and obtain the partial results concerning for example different compartment impacts, human health risk assessments or environmental specific target risk assessments. In particular the aim of ERICA is to provide an instrument that can be used to measure the “no effect” of new compounds emitted into a background contaminated environment. This will be of great help for green technologies and may help industries advertise their products as safe for the environment following impact assessment not derived only from regulatory thresholds values often chosen mainly for political and economic reasons.

The fact that a certain compound added to an existing scenario will not pose additional risk is currently not considered in its overall meaning (environmental risk assessment–health risk assessment–fate and transport) by any legislation, so industries that are able to show also these properties, e.g. design for degradation, will have an added value of their products. Furthermore this will lead to an

awareness by industries that will be responsive of how much their products are impacting on the environment in the most realistic way possible.

The ERICA model may be used by industries and municipalities to monitor and document their overall environmental performance and to quantify long term sustainable industrial emission allowing for long term suitability of land use types in its vicinity. The ERICA innovated tool will be improved to measure the indirect industry impact on human health and it will propose an integrated risk assessment approach to measure the impact of the policy and procedures adopted by the companies and managers addressing human health and environmental protection. The improved index will measure industrial performance with respect to environmental quality and its effects on human health. Its main objective will be to develop a new methodology intended to help industry and regulatory bodies to evaluate the positive effects resulting from mitigation actions and to promote eco-efficiency.

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